ASSESSMENT OF THYROID DYSFUNCTION IN PATIENT RECEIVING WHOLE NECK IRRADIATION IN HEAD AND NECK MALIGNANCIES.

Dr. Poonkodi.N MDRT cancer institute(WIA) Adyar, Chennai.

ABSTRACT

AIM:

To Assess the incidence of thyroid dysfunction in patients receiving whole neck irradiation in head and neck malignancies.it is justified that routinely performed Thyroid function test (TFT) during routine follow up.

Materials and methods:

Fifty patients with locally advanced head and neck malignancies receiving whole neck irradiation for the period of one year were included in this study. Thyroid function tests (TFT) was done at baseline (Before start of treatment), after six months, and at the end of one year interval.

RESULTS:

Out of fifty patients included in this study, 39(78%) were males and 11 (22%) were females. All patients received radiation to neck >40Gy. Among 50

Patients received whole neck irradiation,20 patients had hypothyroidism with significant P value of 0.0001. 35 received chemotherapy concurrently and out of 35 patients 18 had hypothyroidism with 51.42% and 15 patients received only radiotherapy out of 15 patients 2 had hypothyroidism with 13.33%. Among them, 20patients had abnormal values; 15 Patients (30%) were found to have subclinical hypothyroidism and 5patients (10%) developed clinical Hypothyroidism. Out of 15 patients who had subclinical hypothyroidism seven patients in one year follow up and three patients in 6months follow up .In clinical hypothyroidism out of 5patients 4 were in one year follow up, one patient in 6months follow up.In concurrent chemo radiotherapy out of 35 patients 18 had hypothyroidism (51.42%)and in only radiotherapy 2 out of 15patients had hypothyroidism (13.33%),with P value of 0.0137

Conclusion: Thyroid dysfunction usually Hypothyroidism either Clinical or subclinical is a less recognized morbidity of external beam radiotherapy to head& neck exceeding the 40Gy radiation. Detecting hypothyroidism early and treating is preventing associated complications. Hence mandatory to made Thyroid function tests as a routine during follow up.

KEY WORDS:

Head& neck cancer, concurrent chemo radiotherapy, hypothyroidism, Radiotherapy.

1. INTRODUCTION

Thyroid gland is an endocrine gland which is located in anterior neck in front of trachea. It secretes two main hormones

1. T3 (Tri iodothyronin)
2. T4 (Thyroxin),

Essential for **normal growth and development.**

The head cancers incidence fifth ranked in all other malignancies in Indian population probably due to tobacco use in various forms[(1)].The treatment modality for the head & neck cancers are

- Surgery
- Radiation (RT)
- Chemotherapy(CT)
- Combination of these.

RT, besides surgery the only curative option, in the treatment of patients with head and neck cancer. Radiation to thyroid gland in radiation field leads to Hypothyroidism. Most of head and neck cancers were loco regionally advanced at diagnosis so we need to cover whole neck bilaterally along with the primary with adequate margins, to avoid missing neck nodes in the radiation field.

While on whole neck radiation thyroid gland in the neck which is close to head and neck primary sites also included in the field gets irradiated. This is an unavoidable normal tissue complication of external beam irradiation to neck.

Even though this thyroid dysfunction is unavoidable, it can be treated if we found early and morbidity can be avoided. The commonest late effect of thyroid gland radiation in patients exposed to therapeutic neck radiation (>40GY) is **Hypothyroidism[2].**

Clinical Hypothyroidism characterized by high TSH values and low Free T4 and Free T3 values.

Subclinical Hypothyroidism (Biochemical or compensated hypothyroidism): characterized by high TSH and normal FreeT4,Free T3 values.

Subclinical hypothyroidism proceeds to clinical hypothyroidism at a rate of 5 to 20% per yea**r**[3].Though hypothyroidism was associated with significant morbidity, performing thyroid dysfunction is not yet part of follow up of patients even in long-term survivors of head and neck cancer. It resulted in failure to detect and treat a reversible cause of morbidity for those patients. Nowadays with the practice of concurrent chemo radiation increases the loco regional control and increases the overall survival of patient whish increase the incidences of hypothyroidism. Hence the purpose our study to assess the incidence thyroid dysfunction in patients receiving neck irradiation, to assess the mean time for development of primary thyroid failure due to irradiation and to study the usefulness of thyroid function tests in follow-ups and make it as routine follow up.

Evaluation of head &neck cancer treatment

The treatment of head and neck cancer are complex and it is difficult both technically and biologically. The sub sites of head and neck regions originate from the same squamous tissue. The clinical presentation and response to therapy differs for different subsites in addition structures of head and neck essentials for important functions body such as swallowing, breathing and speech. Hence organ preservation is important for selection of treatment for head and neck cancers.

EPIDEMIOLOGY OF HEAD AND NECK CANCER:

Worldwide the head and neck cancer incidence annually was more 550,000 [4] Males were affected more than females with a ratio ranging from 2:1 to 4:1. The incidence rate in males exceeds 20 per 100,000 in regions of France, Hong Kong, the India, Europe, Spain, Italy, Brazil and united states.

The Indians are commonly affected with oral cavity cancers, the nasopharyngeal cancers are common in Hong Kong.

Most of western population were affected with laryngeal and pharyngeal cancers, and accounts for 3%of malignancies (5).Among them 12,000 were dying of disease annually.

Mouth and tongue cancers are more common in the Indian subcontinent, nasopharyngeal cancer is more common in Hong Kong, and pharyngeal and/or laryngeal cancers are more common in other populations.

In the United States, head and neck cancer accounts for 3 percent of malignancies, with an estimated 55,000 Americans developing head and neck cancer annually and 12,000 dying from the disease[6]. The incidence of laryngeal cancer incidence was 50 percent higher in African American men[7].The mortality associated laryngeal and or pharyngeal cancers higher in African American men, reflect the lower prevalence of HPV positivity[8].

HEAD AND NECK CANCERS RISK FACTORS

- **SMOKING**: It is a major risk factor for laryngeal cancers. Tobacco smoking contains more than 30 different types of carcinogen, such as polycyclic aromatic hydrocarbons and nitrosamines.

40cigarette per day associated with 13times increased risk of cancer.

And also patient continues smoke will have second cancers and field concretization chances.

- **Alcohol**
- **Tobacco** chewing.
- Human papilloma virus infection.

AIMS OF TREATMENT

Curative treatment.

Preservation of anatomy and function.

Minimal sequlae of treatment.

Best treatment delivery in cost effective manner.

Modalities of treatment for locally advanced head and neck cancer

- Surgery.
- Radiotherapy.
- Chemoradiation
- Multimodality therapy.

Majority of head& neck cancers locally advanced at diagnosis. Surgery and radiotherapy are the curative treatment options available. Each modalities of treatment have its own merits and demerits.

Radiation advantages:

- No postoperative complication. Functional and cosmetic results maintained because no tissues removed. Surgical salvage of irradiation failure is probably more likely than the salvage of a surgical failure.

The advantages of surgery includes

Similar cure rates like Radiation and also the following:

- Limited amount of tissue is exposed to treatment.
- Shorter treatment time.
- Radiation sequelae will be avoided.

CHEMOTHERAPY:

Introduced later stage to prevent the development of second primary cancers (chemoprevention)

- To palliate symptoms in patients with incurable disease
- To improve the odds of cure or organ preservation when combined with definitive loco regional therapy.

Toxicity vs normal tissue complications in locally advanced head& neck cancer.

The nonsurgical treatment modality for advanced head and neck cancer is concurrent chemo radiotherapy approach.

It improves both loco regional and overall survivalfor patients with locally advanced head and neck cancer, IT CAN BE DELIVERED **SYNCHRONOUSLY** OR IN AN **ALTERNATIVE REGIMEN.**

In modern era the concurrent chemo radiation is one of the treatment modality for locally advanced head and neck cancers for organ function preservation.

Advantages of concurrent chemo radiation:

- ✓Maximize systemic therapy
- ✓Radiation enhancement
- ✓Local and systemic therapy delivered concurrently.

Disadvantages

- ❖ Increased toxicity
- ❖ Increased treatment time.
- ❖ Difficulty in completing radiotherapy.

The chemotherapeutic agent used to improve radiation effect and improve overall survival in head and neck cancers are the platinum group of drugs especially **cisplatin.**

Concurrent chemo radiation

1. The mechanism of interaction between these two modalities of treatment includes following:

2. The formation of toxic platinum intermediates with the in the radiation-induced free radicals, the capacity of cisplatin to scavenge free electrons formed by the interaction between radiation and DNA that may fixate otherwise reparable damage to DNA, a radiation-induced increase in cellular cisplatin uptake,

3. Synergistic effect between cisplatin and radiation because of cell cycle disruption.
4. Inhibition of repair of radiation-induced DNA lesions.

It is radio sensitizing chemotherapeutic agent commonly used in head& neck cancer malignancies.

Even though Cisplatin group drugs does not cause thyroid dysfunction. Normal tissue complications of cisplatin effect on rapidly proliferating cells(mucosa and bone marrow) leads to mucositis and bone marrow depression. Thyroid is late responding tissue to radiation the effect on cisplatin in thyroid tissue not known.

Radiation therapy is one of the modality of treatment for patients affected with cancer. It is used as **curative** as well as **palliative** treatment. It was estimated that over 60% of patients with cancer will have radiotherapy as part of their total course of treatment[4].

Radiation therapy affects **both tumor cells** and uninvolved normal cells; the radiation therapy to the tumor benefit and to the normal tissue detriment of patients.

In recent era of cancer care treatment With the goal of achieving high local regional control of cancer, balancing between the two (cancer cells as well as normal tissue) are both an art and a science of radiation oncology. Unfortunately, after over 100 years of practicing radiation oncology and in spite of much recent progress,, knowledge on either of the two is far from perfect.

Aims of radiation therapy

- Better local tumor control.
- Acceptable normal tissue complications.

2. HISTORICAL BACK GROUND

Wilhelm Conrad Roentgen discovered X-RAY in 1895.First medical use of X-Ray reported in lancet 23rd January, in 1896.(9). He publically demonstrated the clinical X rays radiograph on Swiss professor of anatomy Rudolf Albert von Kolliker ‘s wrist, using X ray beam(fig-1).

Figure 1.first X Ray

Leopold Freund an Australian surgeon who used x-ray for therapeutic purpose, he used for hairy mole-which disappeared after treatment.

In the year 1896 -**Antoine Hentri Becquerel** discovered Uranium-a radioactive material and invented radiobiological effect of radioactive material.(9)

In the year 1898 -**Pierre and Marie curie** isolated polonium and radium, Pierre curie himself produced radium burn on his forearm on 1901. Then radium used for

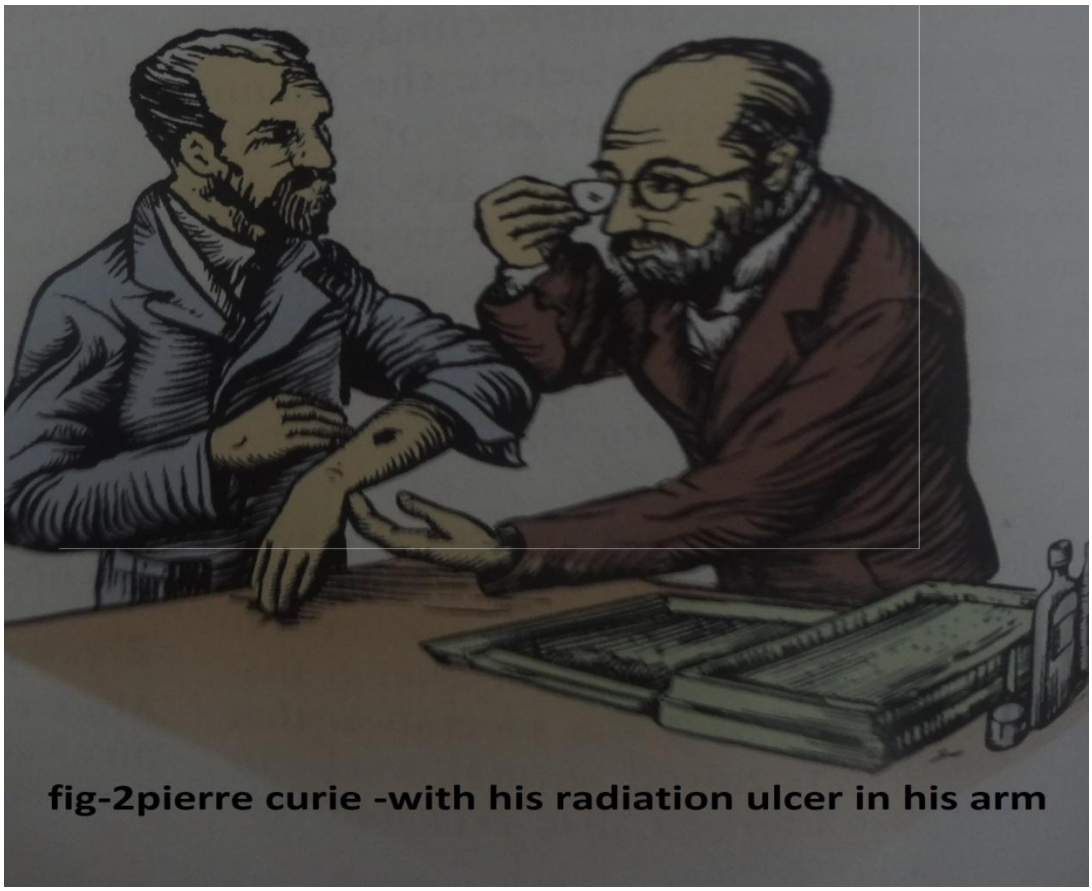


fig-2pierre curie -with his radiation ulcer in his arm

EmilGrubbe, a American medical student (on 29th January 1896)introduced radiation clinically.

EmilGrubbe, son of German couples , coined the term **"radiotherapy"** in 1903:

"He was interested in comparing the effects of phototherapy and radiotherapy"[10].

After that the radiation oncology has developed

- **Radium** was used for the radiation treatment purposes.
- **In a tissue**-balance between cell birth and death to maintain tissue organization**.**
- **The response to cell damage- depends upon**:

    - The inherent cellular radio sensitivity.
    - The kinetics of tissues
    - Ways cells are organized in tissues.

The Fractions of cells are killed- cells lost their reproductive capacity.

If the radiation damaged large amount of cells & killed and removed from the tissues. Radiation damage occurs on the dividing cells.

Radiation damage occur organs like bone marrow & intestinal epithelium Tissues with rapid cell turnover. Occasionally dividing cells like **thyroid tissue**, radiation damage remain latent for a long period and expressed very slowly.

BERGONIE AND TRIBONDAUE[11].

The radio sensitivity depends on:

- The poorly differentiated tissue
- Cells with high mitotic activity.
- Presence of more proliferated cells.

Bergonie and Tribondeaulaw, stated that the effect of radiation on poorly differenciateddivided cells with high mitotic activity is high radiosensitive than

Well differentiated.

From historical point of view, the first formal attempt to address to normal tissue tolerance radiation, was carried out by **Rubin and Cassarett**[12]**..**His publications helped radiation oncologist to buildup of normal tissue complications in future.

In 1980s there was quantum leap of progress in radiation oncology. With monumental work of researchers on four **National Cancer Institute** multi-institutional contracts, the science and practice of radiation oncology Changed from a **two-dimensional (2D)** to a **three-dimensional** (3D)/volumetric process.

The work done by above studies, it became apparent to the clinicians that information on the **tumoricidal doses of radiation** as well as **normal tissue complication doses,** especially on partial volumes, is mostly empirical and totally inadequate. Finally the data

done by them were analyzed by committee addressed for that shows all the data were not consistent.

Moreover, in order to shed some light on the volumetric aspect of these issues, it was decided that organs be divided into one-third, two-thirds, and whole organ volumes. In spite of the clear indication in the manuscript on the paucity of solid experimental/prospectively driven data, this publication, so-called **Emami's paper**, has gained much popularity.

The main goal of this publication was to address a clinical need based on available information up to that time and points to the fact that there is a need for extensive and comprehensive research in this area.

Flaws of the publication:

1. It was a literature review up to 1991.
2. It was completely pre-dated the 3D-CRT, IMRT- IGRT era.**Time dose-volume histograms** - not in routine clinical use.
3. This was a tabulation of the estimates for three of the aforementioned arbitrary volumes

4. This was for external beam radiation with conventional fractionation.
5. Only one severe complication was chosen as an endpoint.

Over the last two decades, since the publication of "**Emami's paper"** the practice of radiation oncology has been completely revolutionized:

- ✓ Multidisciplinary management of cancer -become the standard of care.
- ✓ Choice of an endpoint for complication analysis and modeling has significantly altered.

There has been a major revolutionary change in technology:

CT simulation has become routine along with the fusion of other modalities such as MRI, PET, and 3DCT ,4DCRT/IMRT/IGRT has become standard with the array of evaluation tools.

As a result, dose distributions have become very complex and as of recent, the fourth dimension, namely time, has also been added to this complex.

Multiplicity and complexities of factors affecting radiation including normal tissue complications have made it impossible to have actual data for every clinical situation facing practicing radiation oncologists. Therefore, there is a need for reasonable predictive models for plan evaluation, to improve tumor control, and to predict and hopefully prevent normal tissue injury.

During the last two decades, a vast amount of published information has become available to address the relationship between dosimetric parameters and the clinical outcomes of normal tissues. Because of different analytic methodologies, calculation methods, endpoints, grading schemes, etc., the data is noisy and shifting through these data for practicing radiation oncologists is a nearly impossible task.

Realizing this difficulty and the obvious need for a simplistic format, a group of physicians and researchers were formed with the name **"The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC)."**

The first goal was to review the **available literature of the last 18 years on volumetric /dosimetric information of** normal tissue complication and provide a simple set of data base to be used by busy community practitioners of radiation oncology.

I.	Host	Age Comorbid conditions Host response to radiation Smoking KPS	
II	Organ	Pre-radiation organ condition (Poor PFTs; LFTs; COPD) Regional variation of radiosensitivity with the organ Impact of other organs Hierarchal organization of the organ: Serial: dose effect: spinal cord Parallel: volume effect: lung, liver Both: kidney	
III	Natural history of tumor		
IV	Treatment	A—Radiation Dose (max, min, mean) Fractionation (fractional dose): BED Dose rate Overall treatment time Treatment energy Volume (V dose: absolute or relative)	
IV	Treatment	B—Nonradiation Chemotherapy (drug type, dose, schedule) Radiation modifiers (type, dose, schedule) Surgery (interval)	
V	End points ACUTE	Type: Clinical Radiographical: anatomical, functional Biochemical (blood test, functional test) Degree of severity Degree of frequency Impact on quality of life (QOL)	LATE
VI	Issues on reporting of toxicity		

RADIATION EFFECTS

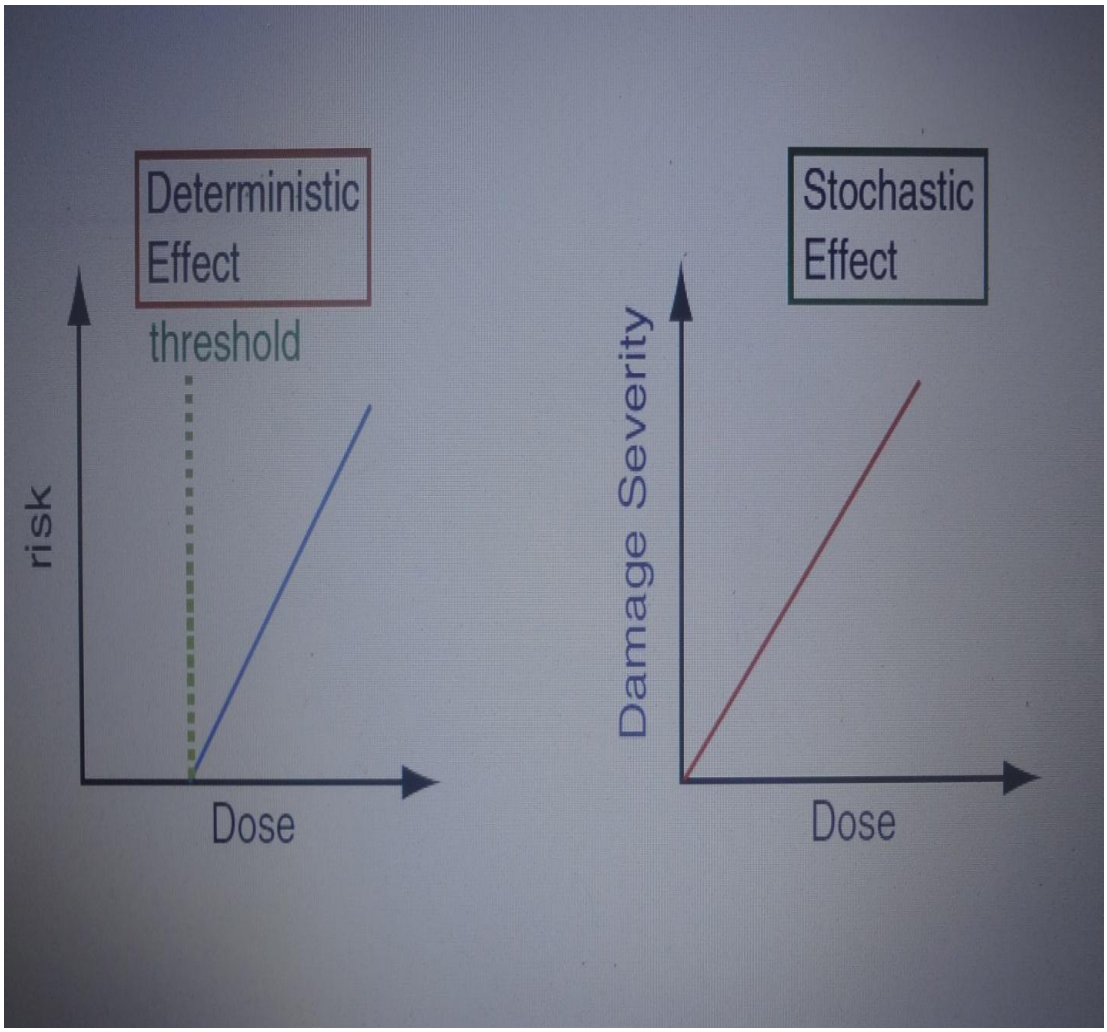


Fig-3 Radiation effect

DOSE RESPONSE RELATIONSHIP OF NORMAL TISSUE AND TUMOR

Radiobiology applied to clinical radiotherapy applied to clinical radiotherapy concerned with relationship between given absorbed dose

and consequent biological responses normal tissue as well as tumor tissue.

ABSORBED DOSE:

Defined as energy imparted per unit mass by ionizing radiation to the matter at a specific point.

ABSORBED DOSE:JOULE/KG OR GRAY.(13)

Radiation effect is directly proportional to radiation dose, increasing radiation will cause increase in grade and incidence of effect. so the relationship between dose and response of tissues are plotted in graph is called dose response curve. This curve is sigmoid shape.

The dose response effect otherwise called as TCP(Tumor control probability), applies to both tumor control and normal tissue complications.

TCP : GRAPHICAL REPRESENTATION[14].

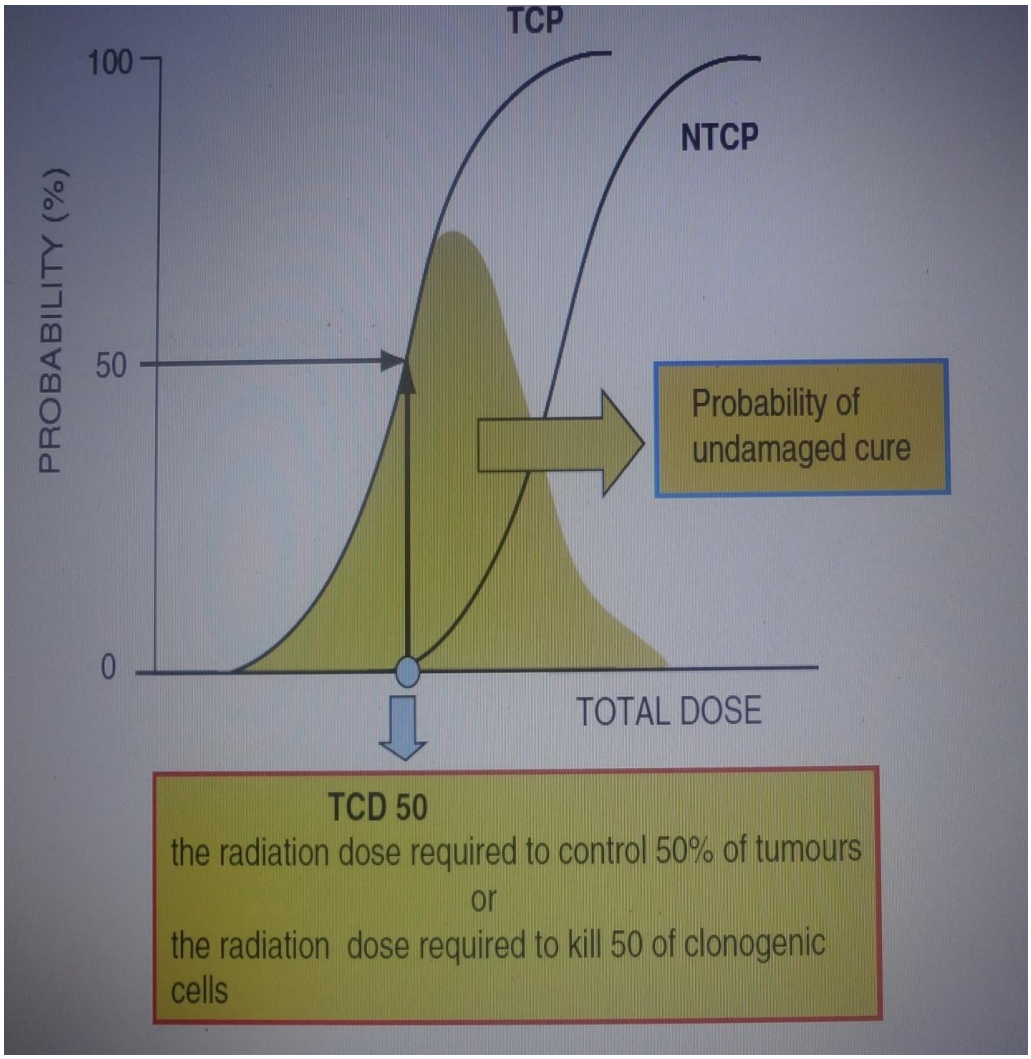


Figure-4.TCP Vs NCTP

THERAPEUTIC INDEX[15].

The ratio of tumor response for a fixed level of **normal tissue damage** called as therapeutic ratio or therapeutic index. This graph

denotes 30% probability of tumor control with 5%incidence of normal tissue complication.

NORMAL TISSUE COMPLICATION AND TIME FACTOR:

Time factor is one of important factor for increasing and decreasing therapeutic ratio. For example.

Hyper fractionation:

This Cause more acute side effects and sparing late responding normal tissues than tumor control, especially thyroid gland like tissues. In TCP curve the addition drug or radio sensitizer will increases the tumor control with less normal tissue complications, this will increases the therapeutic gain. The addition drug move the TCP curve to left father away from normal tissue. This denotes the drug has a greater tumor control with less normal tissue complications.

For example cisplatin use in head &neck cancer have the same effect, but synergistic effects of radiation cisplatin radio sensitizer effect increase the acute toxicity. So in summary the normal tissue complications determined by radiation dose, duration of treatment time, andthe fractionation schedule.

Normal tissue effects of radiation:

- **Acute effects**
- **Late effects.**

Both the above effects in normal tissue caused by cell killing by:

- Release of inflammatory cytokines.
- Depletion of normal tissue population.

TOLERANT DOSE FOR DIFFERENT ORGANS

Organ	**TD 5/5**			**TD 50/5**		
	Whole	2/3	1/3	**Whole**	2/3	1/3
Bladder	6500	8000	N/A	8000	8500	N/A
Brachial plexus	6000	6100	6200	7500	7600	7700
Brain	4500	5000	6000	6000	6500	7500
Brainstem	5000	5300	6000	6500	–	–
Optic nerve	5000	–	–	6500	–	–
Parotid gland	3200	3200	–	4600	4600	
Rectum (severe proctitis,necrosis,fistula,stenosis)	6000	–	–	8000	–	–
Spinal cord	(20 cm) 4700	(10 cm) 5000	(5 cm) 5000	–	(10 cm) 7000	(5 cm) 7000
TMJ mandible	6000	6000	6500	7200	7200	7700
Thyroid	**4500**			**8000**		

The tolerance dose- dependent on

- Total dose
- Fractionation schedule
- Volume of irradiated normal tissue

- TD 5/5 = 5% (probability of severe sequelae in 5 years)

- TD 50/5= 50% (probability of severe sequelae in 5 years)

Thyroid gland

The thyroid gland develops from median outgrowth from the floor of the pharynx near the base of the tongue. The foramen caecum of the tongue indicates the site of origin and the thyroglossal duct marks the path of migration of the thyroid gland to its final adult location.

Anatomy

Both thyroid and parathyroid glands are endocrine glands positioned anteriorly in the neck.

The thyroid gland is a large, unpaired gland. It is lying deep to the strap muscles. Laterally both sides condensation of deep cervical fascia is namely **Berry's ligament.**

Blood supply

Superior thyroid artery:The first branch of the external carotid artery. It divides into anterior and posterior glandular branches:

Anterior glandular branch supplies along the superior border of the thyroid gland and anastomoses with its twin from the opposite side across the isthmus;

Posterior glandular branch passes to the posterior side of the gland and may anastomose with the inferior thyroid artery.

Inferior thyroid artery

The **inferior thyroid artery** is a branch of the **thyrocervical trunk**, which arises from the first part of the subclavian artery.

At the thyroid gland the inferior thyroid artery divides into an:

- **Inferior branch**, which supplies the lower part of the thyroid gland and anastomoses with the posterior branch of the superior thyroid artery;
- **An ascending branch**, which supplies the parathyroid glands.

Thyroid ima artery

Occasionally, a small **thyroid ima artery** arises from the brachiocephalic trunk or the arch of the aorta and ascends on the anterior surface of the trachea to supply the thyroid gland.

Venous drainage

Superior thyroid veins	-	drains into the internal jugular vein.
Middle thyroid veins	-	drains into the internal jugular vein
Inferior thyroid vein(lt)	-	terminate at the left brachiocephalic vein.
Inferior thyroid veins(Rt)	-	drains into the right brachiocephalic vein.

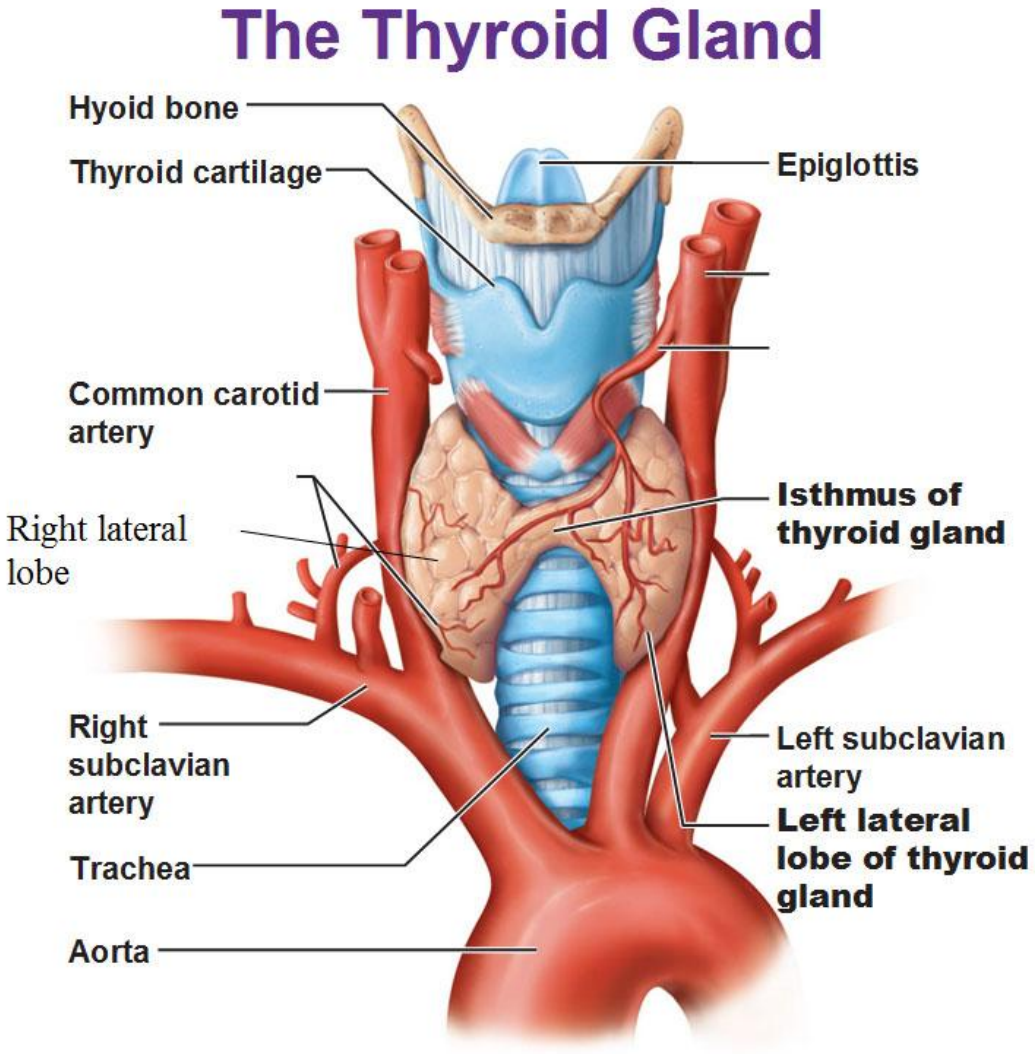


Fig-5 Thyroid anatomy

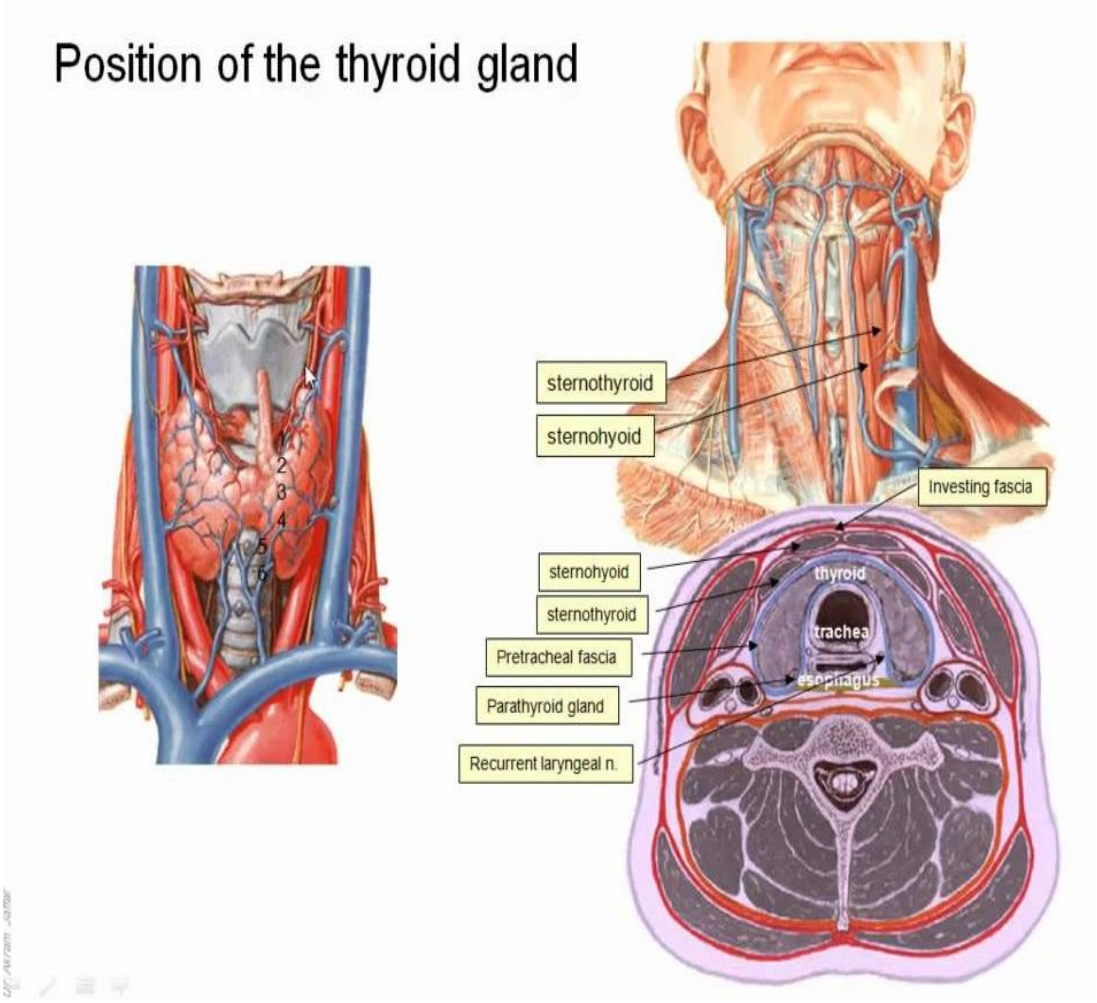
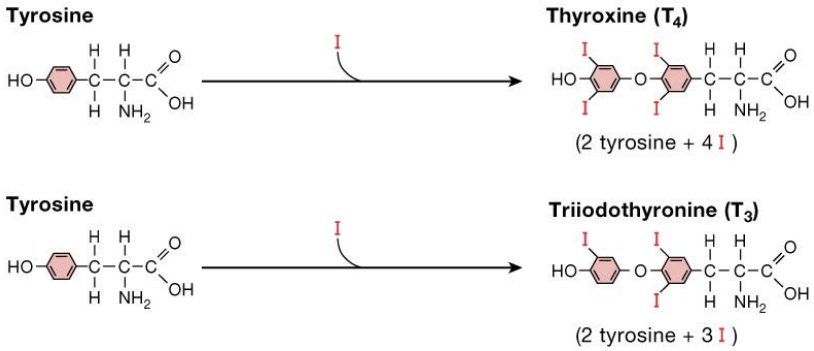


Fig-6 Thyroid anatomy

Formation of thyroide hormones

Thyroid Hormones

- tetraiodothyronine- (thyroxine)
- triiodothyronine (T3)



Production of Thyroglobulin

- TSH, which binds to follicle cell receptors- produce thyroglobulin (glycoprotein).

Thyroid Hormone Synthesis

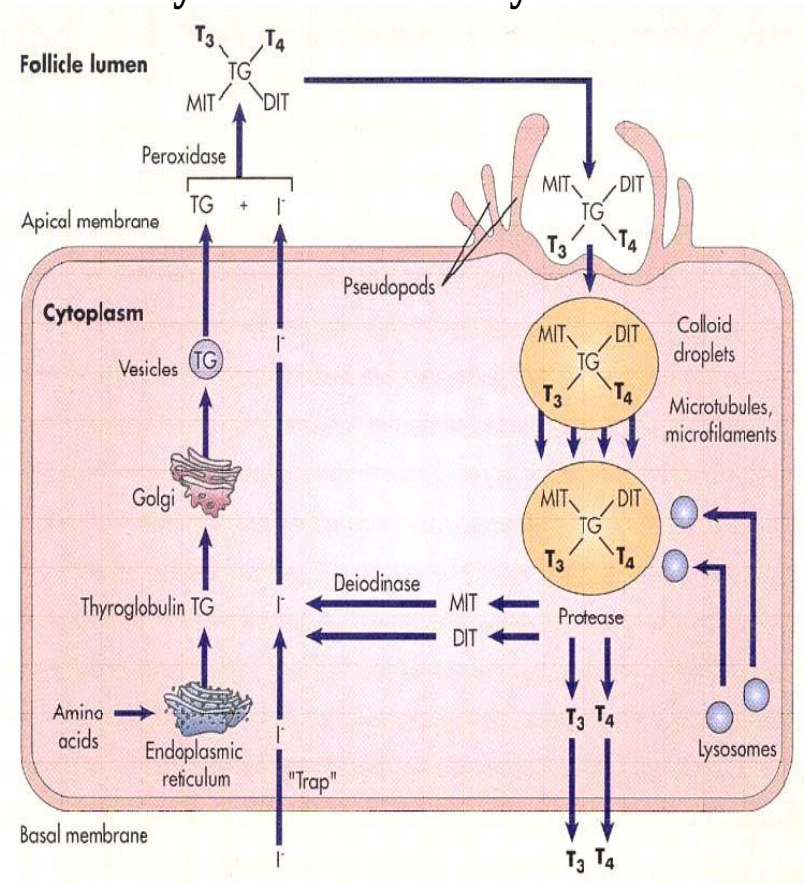
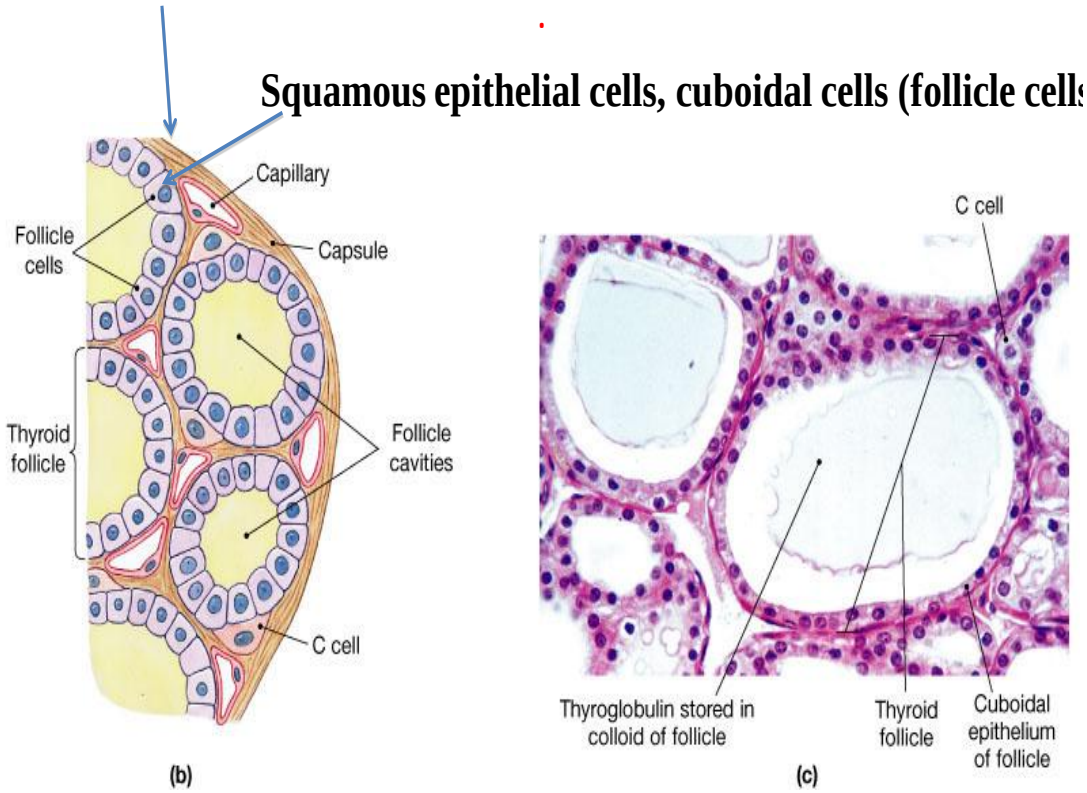


Fig-7 Thyroid hormones metabolism

Transport of Thyroid Hormones.

- Thyroid Hormone-Binding Globulin (~70% of hormone)
- Pre-albumin (transthyretin), (~15%)
- Albumin (~15%)

The Thyroid Gland – Histology



I

Fig-8-. Thyroid gland histology

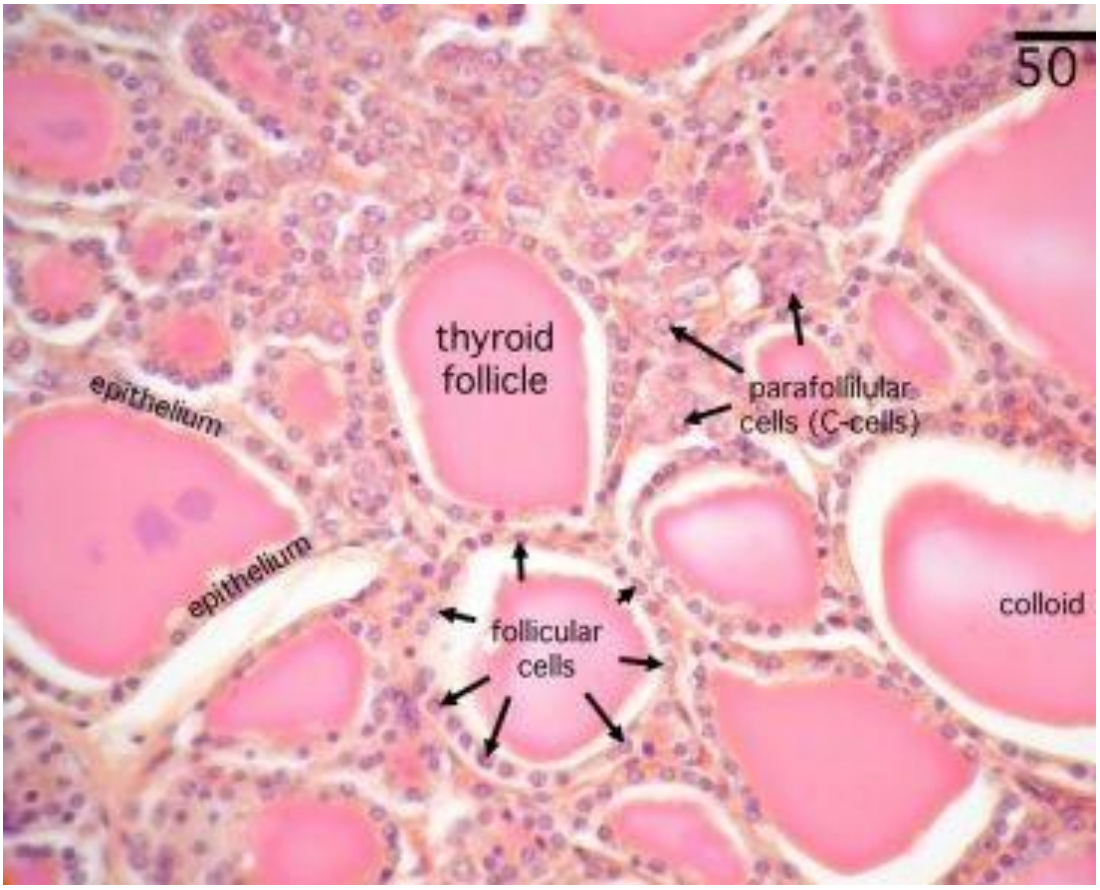


Fig-9. Thyroid histology

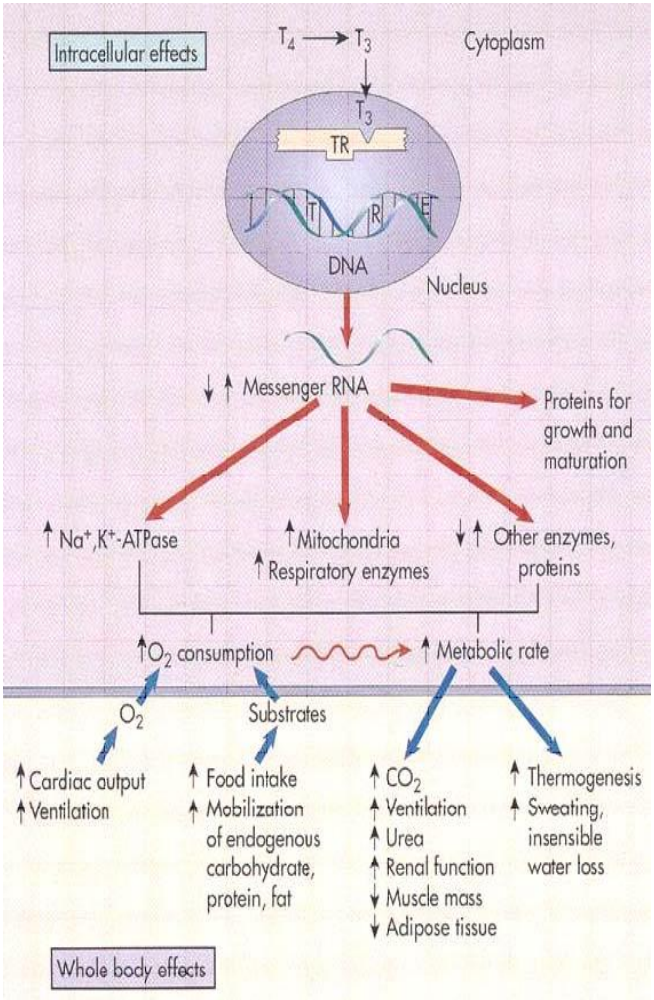


Fig-10. Thyroid hormones metabolic effects.

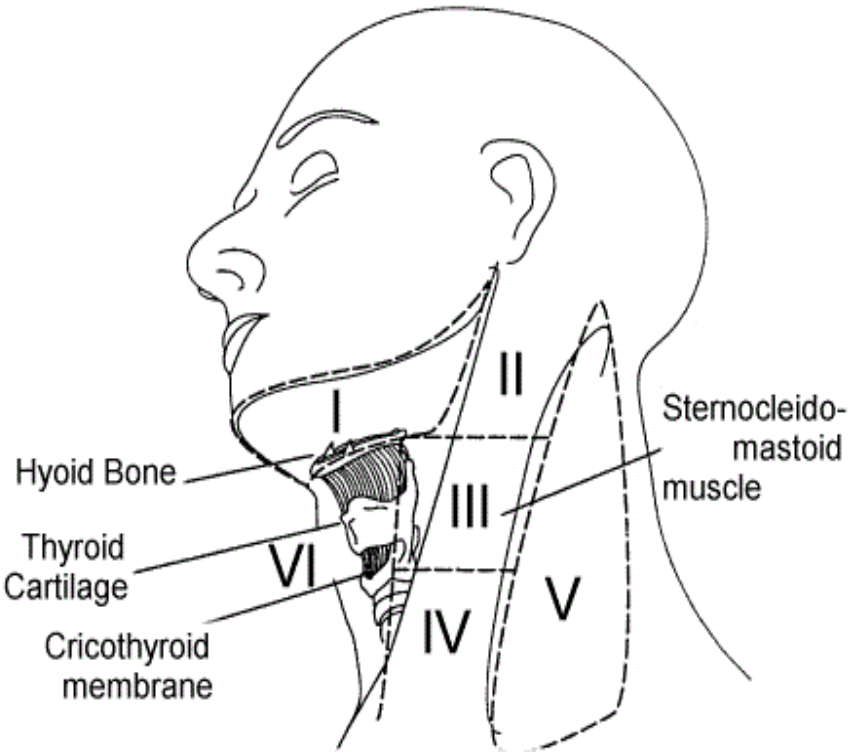


Fig-11. Cervical nodes-Levels.

Level I- Submental and submandibular nodes.

Level II- Uppper jugular nodes.

Level III-Mid jugular nodes.

Level IV-Lower jugular nodes.

Level V-Posterior triangle and SClnodes.

Level VI-Anterior compartment neck nodes.

Level VII-Superiormediastinal nodes.

Thyroid cellular biology:

Hypothyroidism or hyperthyroidism can develop after radiotherapy especially hypothyroidism. Hyperthyroidism results from Grave's disease or thyroiditis and the latter usually results in subsequent hypothyroidism. The manifestations of hypothyroidism are outlined in the preceding section. Hyperthyroidism is characterized by heat intolerance, weight loss, insomnia, increased appetite, diarrhea, moist skin, tachycardia**, nervousness**, tremors, exophthalmos, and goiter. Thyroid enlargement, and more frequently, thyroid nodularity, can also develop.

- **Time Course of Events:** The time course of developing late thyroid effects is highly variable. The risk for both hypo- or hyperthyroidism reported in one study increased in the first 3 to 5 years since diagnosis, whereas the risk for nodules increased at 10 years from diagnosis.

- **Dose/Time/Volume**: Hypo- or hyperthyroidism results from fractionated radiation >20 Gy to the neck or cervical spine, or >7.5

Gy of TBI. Thyroid nodularity can occur after lower dose exposures. Recent data on patients with head and neck cancer support a radiation dose-response for hypothyroidism.

- **Chemical/Biologic Modifiers**: In children treated for Hodgkin's disease, the addition of chemotherapy to radiation does not appear to increase the risk of hypothyroidism, although chemotherapy alone can result in hypothyroidism.

- **Radiologic Imaging:** Thyroid nodules should be assessed by ultrasound, and an I-125 scan can be considered.

- **Laboratory tests:** Free T4 and TSH should be used to monitor thyroid function.

- **Differential Diagnosis:** Grave's disease, Hashimoto's thyroiditis, and idiopathic thyroid nodules can occur in the general population. Patients undergoing cranial irradiation may have neuroendocrine deficiencies (namely TRH deficiency) as previously discussed.

- **Pathologic Diagnosis:** Fine-needle aspiration of newly diagnosed thyroid nodules, particularly those that do not demonstrate I-125 uptake, is suggested. Suspicious nodules or biopsy-proven thyroid cancer should be resected. Interpretation of the fine-needle aspiration may be confounded by radiation-induced atypia.

Management: Thyroid shielding during therapeutic radiation should be considered if possible to lower the risk of late thyroid toxicity. Hypothyroidism can be managed with thyroxin replacement, and hyperthyroidism can be managed with propylthiouracil (PTU), propanol I-131, or thyroidectomy. Thyroid nodules should be managed as previously described.

- **Follow-up:** Routine examination of the neck should be performed to assess for nodularity and/or growth. The NCI recommends annual laboratory assessment up to 10 years post radiation

The reason for hypothyroidism common in Females in general population:

- .In females estrogen(estradiol) effect on thyroid hormone functioning by antagonizing or competing the binding sites

for T4 and T3.If the estradiol finds first to thyroid hormone receptor it will suppress thyroid hormone secretion and leads to hypothyroidism.

- Estradiol also limits the thermogenic activity of thyroid stimulating hormone (TSH), their by reduces the muscular activity and increase the fat deposition in females.

- The another mechanism why females has the tendency to have hypothyroidism is by Autoimmune disorder, so female has more prone for autoimmune disease their by destroying thyroid gland leads to its deficient activity.

- Females eat very less, their calorie intake is very low compared to men ,less fat consumption leads to decreased productionhormones suchas,cortisol,aldossterone,progesterone,estradiol,testostero ne,etc. Likewise less protein intake leads to decreased peptide hormone production like thyroid hormones .So adequate fat and protein intakes also essential for our body hormones

secretion. Thyroid hormones consist of the amino acid tyrosine combined with 1, 2, 3, or 4 atoms of iodine (hence, they have names such as tri – iodo- thyronine).

- Some food items especially soy foods are goitrogenic.
- More stress leads to hypothyroidism by decreased thyroid hormone secretion.
- Finally the cause may be idiopathic.

The reason for hypothyroidism common in neck irradiated female patients:

1.**Autoimmunity:**

Radiation induced hypothyroidism is a organ specific autoimmune disorder, causing epithelial damage as well as necrotizing vacuities and thrombosis. Injury to the epithelial tissue leads to release of thyroid cellular components that acts as a triggering antigenic stimulus leads to production of organ specific Auto antibodies and leads to initiation of autoimmune process and thyroid dysfunction.

In autoimmune mechanism their must by sustain release of auto antibody following antigenic stimuli a genetic susceptibility must be present.

In females it is present in Ir-1 lies within the majority histocompatibility complex.

In males it is HLA-8 association has been demonstrated for autoimmune mechanism.

Tamura et al demonstrated raised antibody titer following irradiation then they subsequently become hypothyroid.

2. Vascular damage: Leads to necrotizing vacuities and thrombosis.

3.**Parenchymal damage:**

Leads to thyroid dysfunction by epithelial injury and destruction of parenchyma.

3. Review of literature

Impact of RT on thyroid function was first reported in 1929[1]. There is no clear cut data is not available for post RT thyroid failure. Most of the reports on thyroid disorders following RT are mostly retrospective. This lacks pre *vs*. post irradiation evaluation that includes small patient populations. Long term follow-up is not available even in long term survivors.[16,17.]

Most of cases were proceeded from subclinical hypothyroidism to clinical hypothyroidism[5]. Subclinical hypothyroidism progressed to clinical hypothyroidism occurs at a rate of about 5 to 20% per year.

Complication of \subclinical hypothyroidism were less well established and most of the literature estated that adverse consequences such as cardiac dysfunction and other subclinical hypothyroid symptoms progress to clinical hypothyroidism[18,19]. Thyroxin supplementation improves cardiac function in subjects with subclinical hypothyroidism.

High magnitude and duration of increased TSH, increase the probability of progression to clinical hypothyroidism. Hence diagnosing

and treating the patient with subclinical hypothyroidism, potentially benefits the patient.

Detecting subclinical hypothyroidism at an early stage will preventclinical hypothyroidism also its morbidity[20].

FELIX and MERHERSON -s1960s reported the development of hypothyroidism after RT for head & neckmalignancies[21,22]. I**ncidences of hypothyroidism following RT were between 3 to 47.**Thyroid dysfunction occurs within months to years after external beam radiotherapy to neck.**%. An incidence of 20 to 30% has been reported by most investigators[23]**

The study with the longest follow-up studied by **Einhorn and Wikholm. With 10-year follow-up of 41 patients of Ca -larynx and Ca-hypo pharynx, treated with RTand found the incidence of hypothyroidism was 7.3%[24].**

Glatstein*et al*. published the high incidence of primary thyroid failure in patients who were treated with radiation for Hodgkin's disease and malignant lymphoma[15]

Alterio*et al*. mentioned radiation-induced late effects, especially thyroid disorders are underestimated. Primary hypothyroidism was the most frequent late effect with an incidence of 20 to 30%[16].

Emami*et al*. reported -tolerance values of 8/5, 13/5, and 35/5 (incidence of clinical hypothyroidism in 8%, 13%, and 35% of patients at 5 years) at the level of 45, 60, and 70 Gyrespectively[25].

Srikanth etalreported mean age was 60 years. Men were highermean age (58.78 years) as compared with women (52.13 years). These patient characteristics were same as published by **Tell R et al andAich RK et al.**Most of the cancers were Ca-hypopharnx(36.5%). **Aich** had a higher percentage of cancers arising fromthe larynx (49%).All the patientsreceived whole-neck irradiation and hence the primary site of the tumor was not a significant factoruniformity in the volume of thyroid irradiated..

Aich showed 21% incidence with concurrent chemoRT as compared with16.6% with RT only.

4. AIM OF THE STUDY

- The incidence of Hypothyroidism,
- The time to required become hypothyroid
- Dose of RT related with development of hypothyroidism
- And whether there any patient related and treatment related factors that are predictive for the development of hypothyroidism
- The use of concurrent CT &RT(whole neck radiation) patient or only using RT being assed for development of hypothyroidism.

4. MATERIALS AND METHODS

Fifty patients with head & neck malignancies receiving whole neck irradiation were included in this study compared with 25 breast patients receiving radiation to chest wall and Breast only. Thyroid function tests (TFT) are done at baseline, (before Radiation, concurrent CT/RT) at 6 months and 12 months intervals.

The cases includes patients with locally advanced malignancies of

1. Nasopharynx.
2. Hypopharynx.
3. Oropharynx.
4. Oral cavity- which needs whole neck radiation.
5. Larynx.

The controls includes:

1. Patients receiving irradiation for breast cancers(Excluding neck).

These patients are selected and thyroid function test was done using CLIA(Chemiluminenceimmunoassay) technique, at 0,6,12 months interval. Results were observed for cases and controls, and statistical significance was Assed using **FISHCER EXACT TEST**-,

FISHER EXACT TEST

	Class-I	**Class-II**	**Total**
Sample 1	A	B	a+b
Sample 2	C	D	c+d
Total	**a+c**	**b+d**	**N**

If there were no systematic association between the variables A and B the population from which the cell frequencies are randomly drawn, the probability of any particular possible array of cell frequencies, a,b,c,d given fixed values for the for the marginal totals a+b+c+detc, would be given by hyper geometric rule

$$\mathbf{P}_{(\text{outcome})} = \frac{(a+b)!\ (c+d)!\ (a+c)!\ (b+d)!}{N!\ a!\ b!\ c!\ d!}$$

In performing factorial operations

recall that 0!=1 and 1!=1.

Also the degree of disproportion with any array of cell frequencies-in effect, the degree of ostensible association between variables A and B within the sample-canbe measured by absolute

difference.

Two tailed probability would be that sum plus the sum of the separate probabilities for the arrays of equal or greater disproportion at the other extreme.

Head & neck arm :

Immobilization is done with the help of Thermoplastic Head & Neck mould(fig-2). All the patients are made to undergo CT scans (5mm cuts) starting from vertex to carinal region.

Figure 12.Immoblization & for head&neck CA.

For all head and neck patients immobilization done with the help of thermoplastic head and neck mold ,the purpose of immobilization are patient reproducibility and correct dose delivered to tumor and avoiding normal tissue complications.

The data sets are then transferred to TPS and the dose to target and Thyroid are then determined. Those patients whose receive <40Gy to thyroid are excluded from the study.

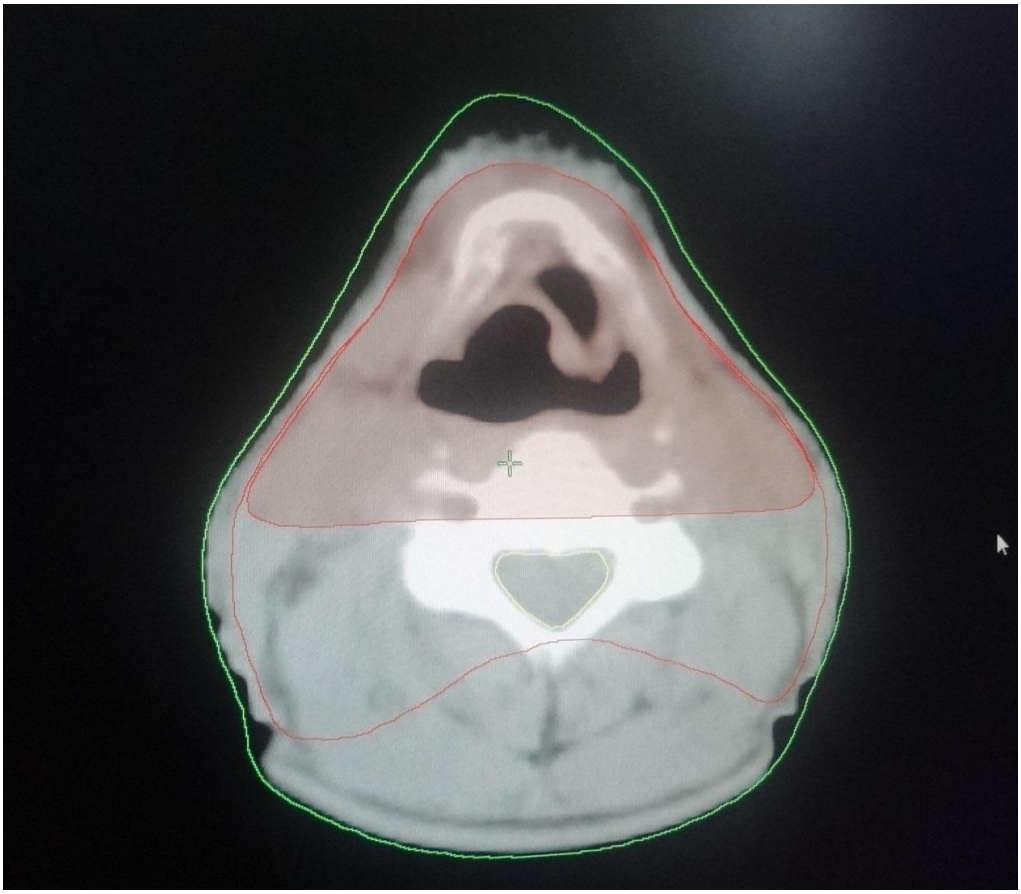


Figure-13.contouring for target & thyroid

This is the picturing showing **PTV(**planning target volume) for patient affected with hypo pharynx cancer .The PTV includes the primary and bilateral neck nodes.

DOSE VOLUME HISTOGRAM

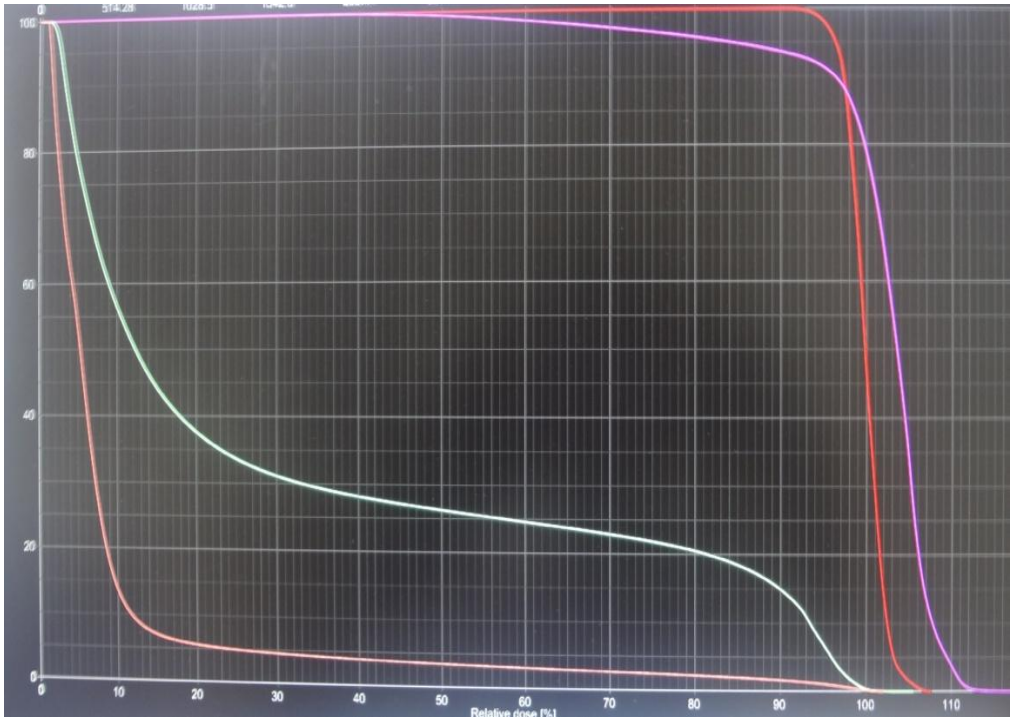


Figure-14.DVH HEAD& NECK

Dosevolume histogram is angraphicalrepresentation providesquatitative information with regard to how much dose is absorbed in how much volume of tissue.It also summarise entire dose distribution into a single curve for each anatomical structure of interest.

TYPES

1. Cumulative interagral DVH.
2. Differencial DVH.

Breast arm:

Immobilisation done with the help of thermoplastic breast mould.

Figure-15.Breast immobilization

Picture showing patient immobilized with thermoplastic breast mould with breast board. Patients are made to undergo CT scans(5mm cuts) starting from neck to upper abdomen. The data then transferred to the treatment planning system and dose to target determined.

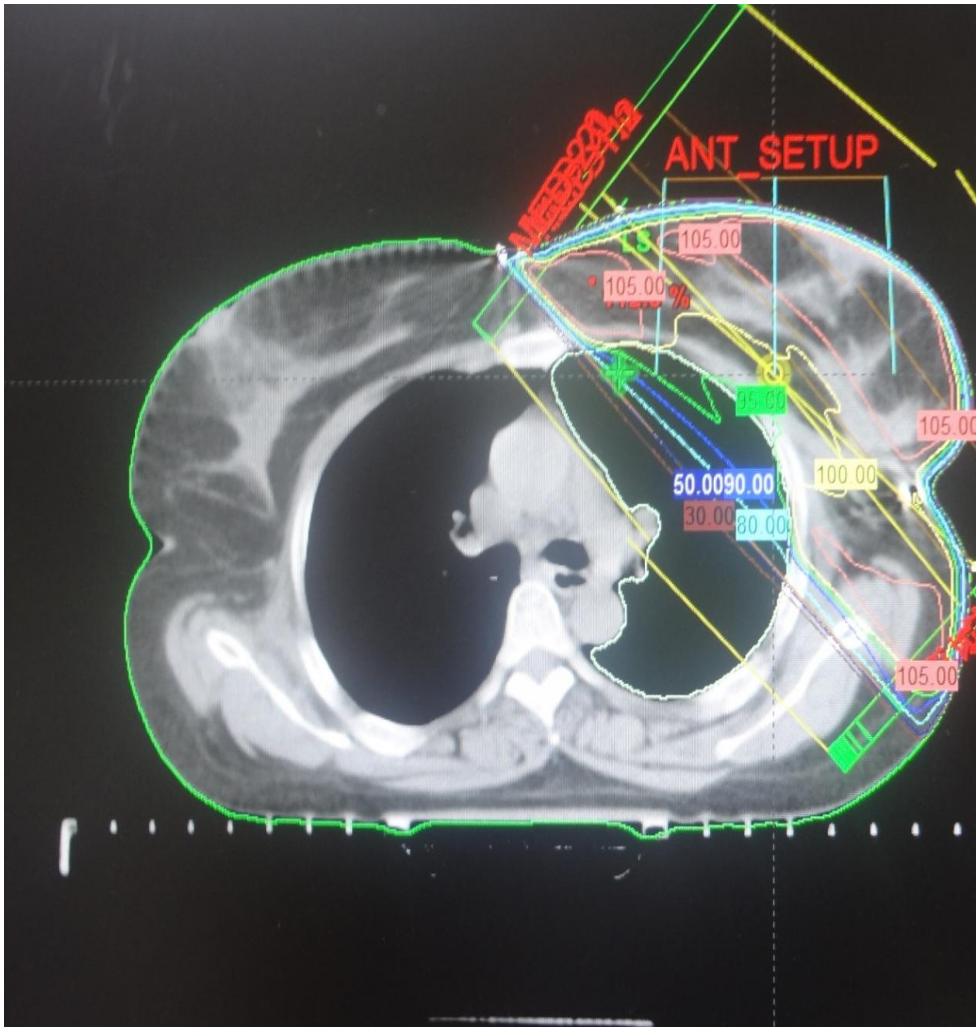


Fig-16. Breast contouring.

This shows planning target volume patient with breast cancer, The PTV includes primary with margin.

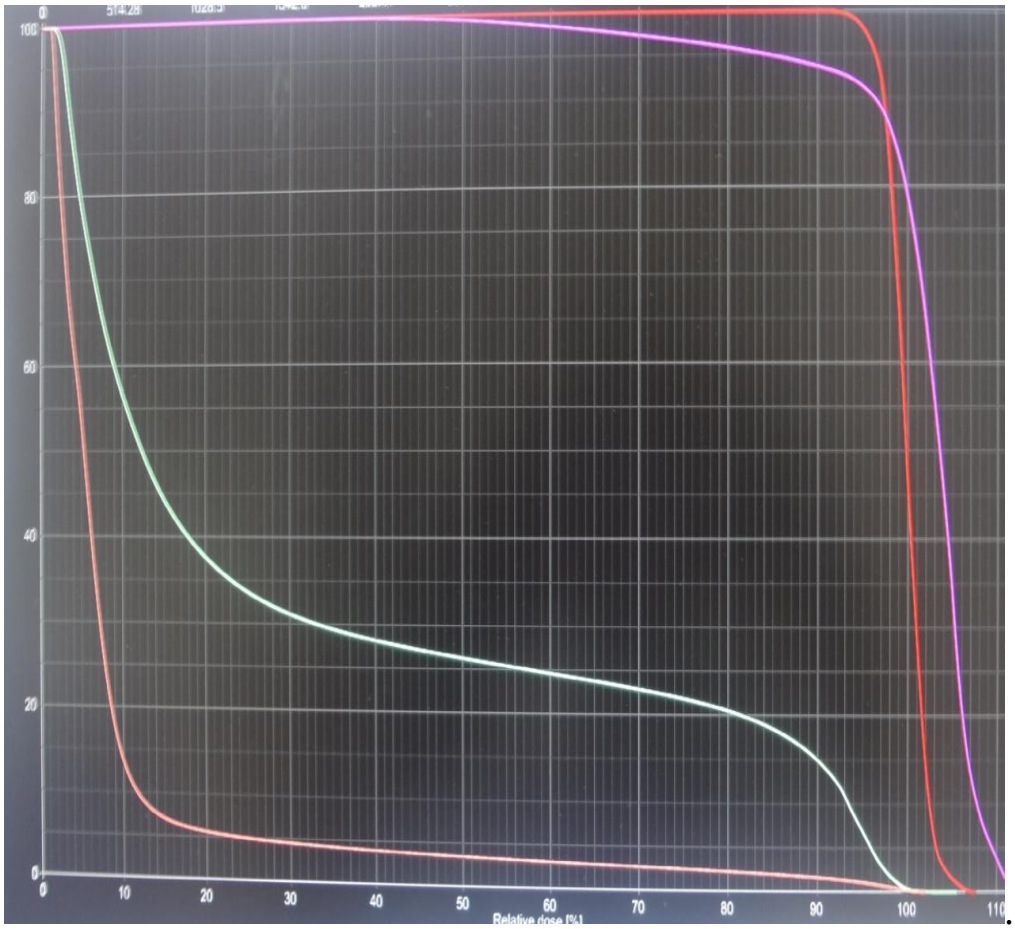


Fig-17. Breast dose volume histogram

Detection of hypothyroidism (sub clinical or clinical)-as primary end point of survey.

Patients who are detected to have hypothyroidism(sub clinical or clinical), after external beam radiotherapy are made to be **reviewed by Endocrinologist** and appropriate supplementation with **Thyroxin** was done.

INCLUSION CRITERIA

1. Baseline TFT should be normal.
2. Patients should receive whole neck irradiation with or without chemotherapy was taken as one arm.
3. Patients receiving irradiation for breast cancers(Excluding neck), was taken as control arm.
4. All ages and both the sexes are included.

EXCLSION CRITERIA

1. Patients with previous thyroid surgeries.
2. Previous irradiation to neck region.
3. Previous thyroid diseases.
4. Recurrent thyroid diseases.
5. Dose to thyroid < 40Gy.
6. Baseline thyroid dysfunction

STUDY DESIGN

Prospective case control study.

STUDY PERIOD

September’2013 to November’2014.

6. Results of the study

In our Single institution, Prospective case control study

From Head & neck, 50 patients were selected as per the inclusion criteria in **study arm,** and 25 patients with breast carcinoma were selected as per the inclusion criteria in **control group.**

The TFT was taken **0 , 6, 12** months interval.

Thyroid dysfunction (either clinical or subclinical) was taken as primary end point and patients were treated with appropriate dose of Thyroxin as per the Endocrinologist opinion.

The results of the study was detected and analyzed with various factors such as Age, Sex and dosimetry and statistical analysis was done using **EXACT FISCHER TEST.**

In our study we found some patients having neuropsychiatric symptoms such as depression, irritability which was mostly neglected by the relatives and these patients underwent evaluation of thyroid function.

By this study, we like to ensure that all subclinical hypothyroidism patients are needed to be supplemented with oral Thyroxin to prevent progression to clinical hypothyroidism and its consequences, as a primary prevention.

In our study we took 50 patients who were underwent whole neck RT, as a treatment for head & neck malignancy.

Patient characteristics

Total patients studied : 75

Head& neck : 50

Breast : 25

Sex distribution

Sex	**Head& neck**	**Breast**
Male	39	0
Female	11	25

Table-1. Sex distribution

Thyroid dysfunction is most common in general population with the percentage of 0.02%.

Irradiation of head &neck primary includes thyroid gland in radiation field leads to unavoidable radiation effect due close proximity of thyroid gland to head & neck primaries, leads to thyroid dysfunction and its long term consequences.

Most of literature reviews quoted that thyroid dysfunction especially hypothyroidism occurs at an earlier stage that is 6 weeks after radiation to 3 to 5yrs .In our study we found out thyroid derangement in 6 and 12 months post RT to neck.

Head and neck cancers are male preponderance, hence 39 male patients and 11 female patients fall in our study .

In our Study - **Post RT head & neck arm** 40% of patients developed hypothyroid. Females were affected almost all patients (10 out of 11) ,

In control arm the **post RT – breast**, all pts are females and no males were taken because of low incidence of male CA Breast. But without the neck RT, none developed hypothyroid in the breast Ca control group.

So irradiation to neck includes thyroid gland in field leads to irradiation of thyroid gland which receives radiation dose above the threshold level leads to thyroid dysfunction which is the late irreversible normal tissue complication of radiation effect.

This signifies the importance of routine screening of TFT in all patients receiving neck irradiation. But the females has a tendency to become hypothyroid early than males, where the hypothyroid was developed at little slower rate and low percent compared with females, with statistical significance, in our study.

In our study we recommend to screen all the patients who received the neck radiation with TFT 6, 12 monthly intervals with baseline Thyroid Function Test.

Demographic data

In our study, on evaluation results were found to be 40 % patients had developed hypothyroidism, among this 10 % were clinical, as well as none developed in the control breast arm.

	Hypothyroidism	**Normal thyroid**	**Total pts**
Head&neckCa	20	30	50
Breast Ca	0	25	25

Table -2.Incidence of hypothyroidism.

P value <0.0001 (0.000067). P value signifies that hypothyroidism strongly associated with head & neck RT.

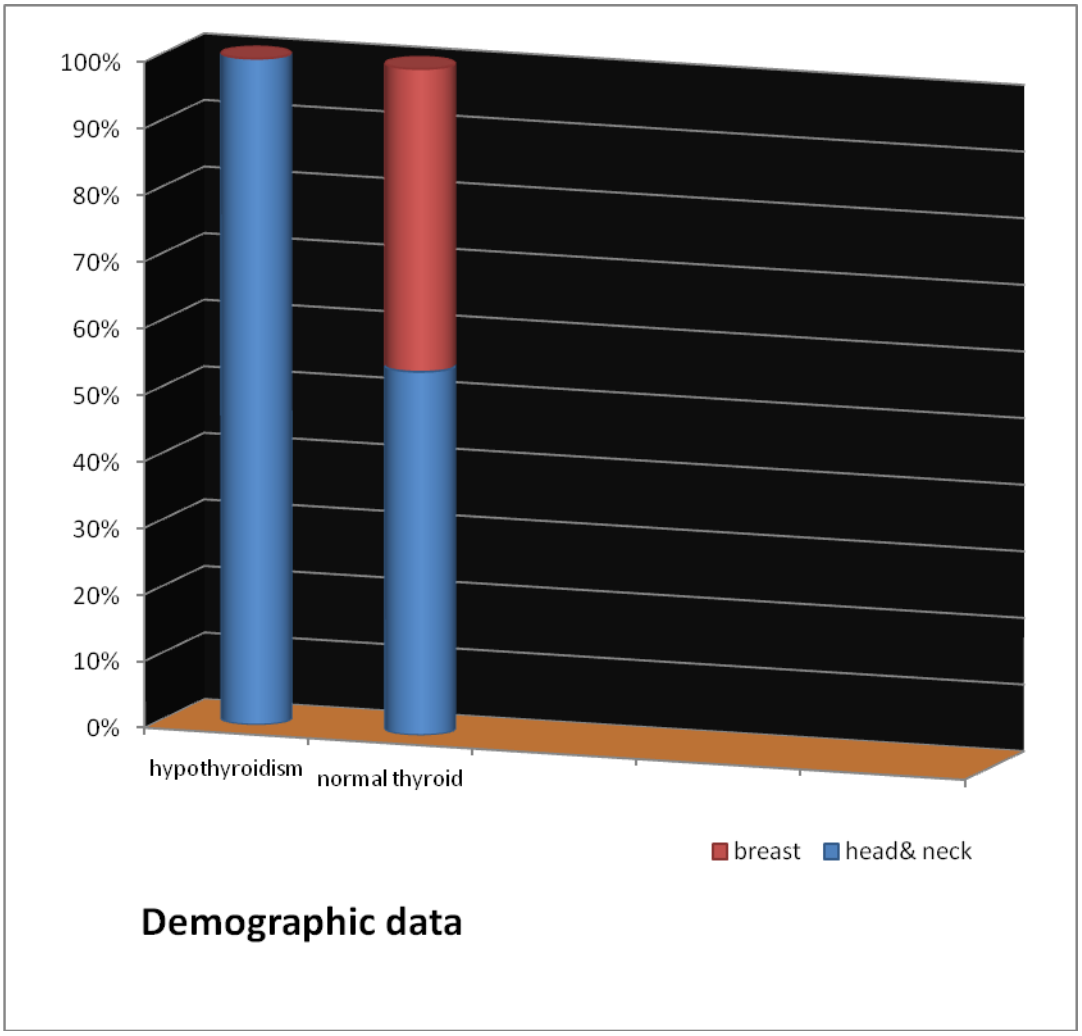


Figure – 18

This bar diagram showed the statistical significant noted that head & neck RT is strongly associated with development of hypothyroidism.

Sex distribution for the head and neck arm

SEX DISTRIBUTION	SUBCINICAL HYPOTHYROID	CLINICAL HYPOTHYROID	NO HYPOTHYROID	TOTAL
MALES	9	1	29	39
FEMALES	6	4	1	11
TOTAL	15	5	30	50

Table-4 .Sex distribution for the head and neck group

P <0.001(P=0.000152). It signifies that the females were strongly associated with developement of hypothyroidism.

Sex distribution for the Breast arm

SEX DISTRIBUTION	SUBCINICAL HYPOTHYROID	CLINICAL HYPOTHYROID	NO HYPOTHYROID	TOTAL
MALES	0	0	0	0
FEMALES	25	0	25	25
TOTAL	25	0	25	25

Table-5. Sex distribution for the Breast arm

In our study, among 50 patients 39 were males represents 78% and 11 were females represents 22%. In Breast arm 100% females are taken for our study.

And 20 out of 50 patients in head and neck arm found to have hypothyroidism which represents 40%.Among this 2/3 are sub clinical and 1/3 patients are clinical hypothyroid.

And breast arm, all female patients developed neither subclinical hypothyroid nor clinical hypothyroid. And in our study found that the strong statistical association noted in irradiated females who were developed hypothyroidism than their male counterpart.

In sex ratio analysis out of 50 patients 20found to have hypothyroid, among them in males 10 out of 39 found to be hypothyroid and in females 10 out of 11 found to be hypothyroid, this shows more female preponderance. In general population the incidence hypothyroidism in general population is 0.02% per year(27)which also has the female sex has a preponderance..

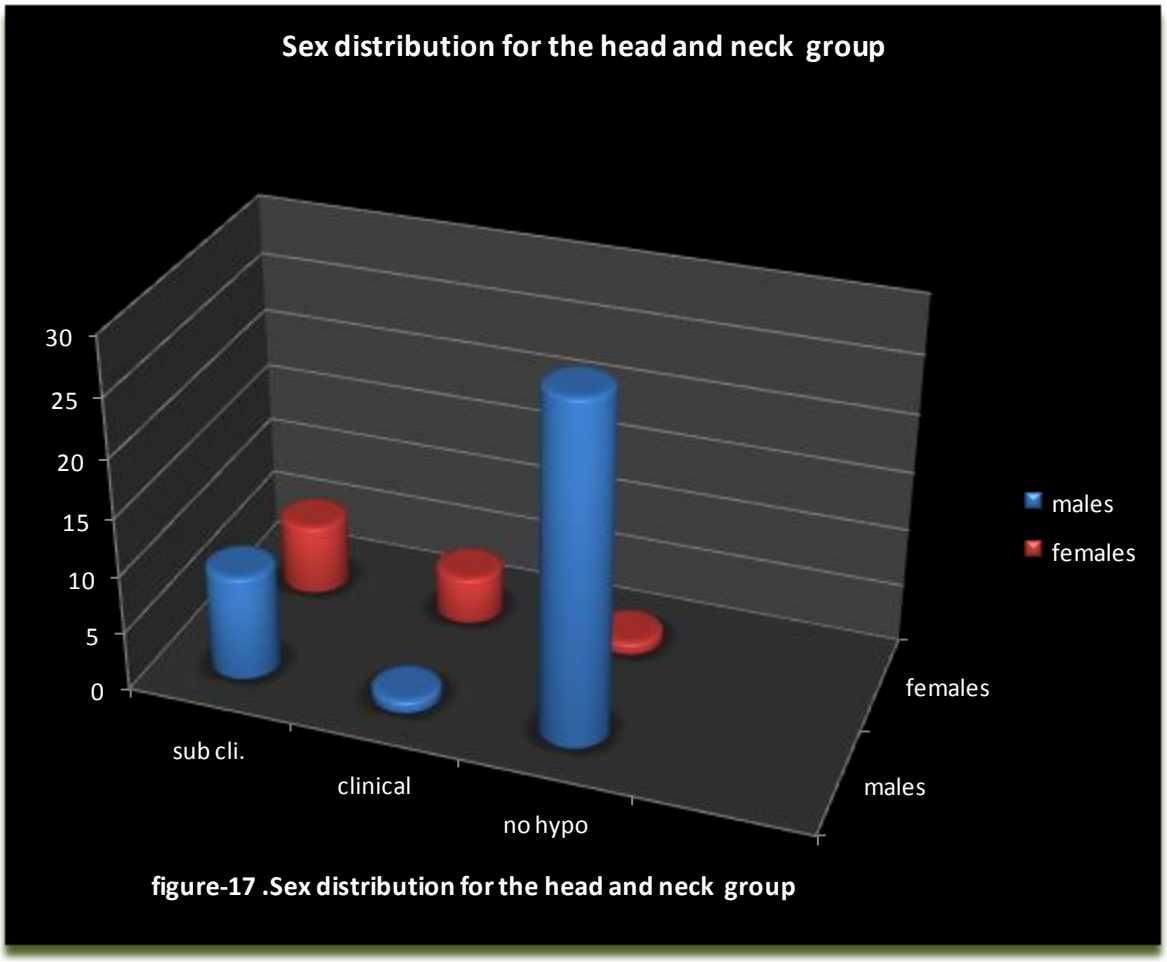


figure-17 .Sex distribution for the head and neck group

In the **Bar diagram**, we notice the subclinical thyroid was proceeded by the clinical illness.

Females were affected by subclinical at an earlier stage then proceeded to clinical hypothyroid in a descending order. Also detected that almost all female needsthyroxine supplementation at 6- 12 month interval.

Males also significantly had thyroid dysfunction, but head&neck cancer incidence are more common in male population. In this study showed the incidence is less comparable to males than females. We also found that thyroid dysfunction developed at the last quarter of year.

So this sex ratio incidence of thyroid dysfunction denotes screening for thyroid in patients of neck irradiation is mandatory in earlier and at regular intervals for long term survivors of locally advanced head& neck cancer.

Age distribution.

The table shows the age was subdivided into 4 category .

AGE DISTRIBUTION	SUBCINICAL HYPOTHYROID	CLINICAL HYPOTHYROID	NO HYPOTHYROID	TOTAL
20-35	0	0	3	3
36-50	4	2	0	6
51-65	11	3	19	33
>66	0	0	8	8
T0TAL	15	5	30	50

Table-3.age distribution

In our study the age groups of patients studied between 20 to >66yrs of age with the **mean age for males were 52yrs**, and the females were 59yrs.

The incidence of hypothyroidism was 14 out of 20 were in the age group of 51-65 yrs of age group, and 6 out 6 in the age group of 36-50 yrs age. This analysis showed the incidence of hypothyroidism is common in elderly and young age group.

The study done by **Bonato and colleagues'** showed the incidence of hypothyroidism in the childhood survivors who received radiotherapy to neck.(13)

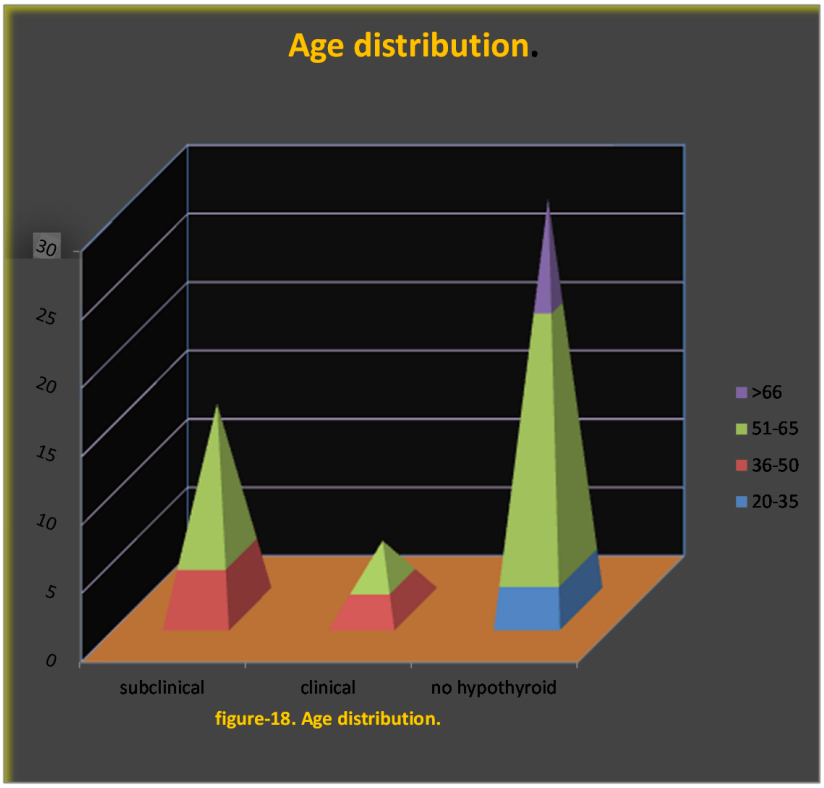


figure-18. Age distribution.

This is due to radio sensitivity of thyroid tissue decreases with the age.

In our study we found that the radio sensitivity was inversely proportional to the age. None of the aged above 66 developed hypothyroidism.

The another study **Colevas et al** stated the increase incidence of hypothyroidism in patients in 60yrs of age group.(14)

In our study showed the incidence of hypothyroidism is higher in young as well as elderly age groups.

Chemo RT Vs only RT

	SUBCINICAL HYPOTHYROID	CLINICAL HYPOTHYROID	NO HYPOTHYROID	TOTAL
CONCURRENT CT/RT	13	5	17	35
ONLY RT	2	0	13	15
	15	5	30	50

Table-4 chemo RT Vs RT only

Out 50patients studied 35 patients received concurrent chemoradiation and 15 received only radiotherapy. Among 35 in concurrent CT+RT group 18 had hypothyroidism.

Only RT group 2 out of 15 had hypothyroidism.

In patients received concurrent CT/RT 51.42 % pts developed hypothyroidism,and patients received only RT developed 13.33 % .

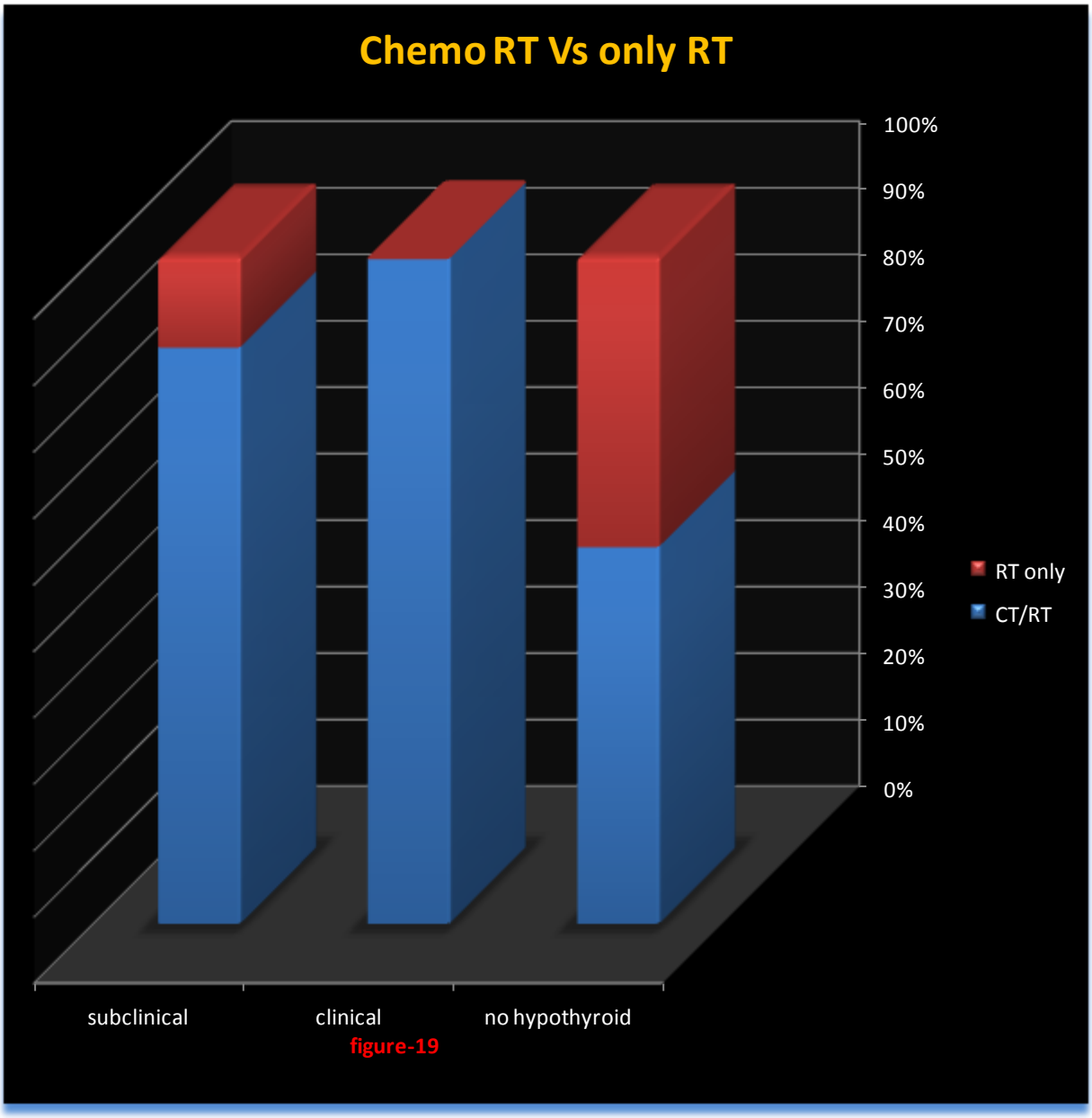


figure-19

In the bar diagram : Concurrent chemo radiation group had more hypothyroidism compared to only radiation therapy group.

In our study group concurrent chemo radiation group received cisplatin based chemotherapy along with RT.

Cisplatin: It is radio sensitizing chemotherapeutic agent commonly used in head neck& cancer malignancies.

Even though Cisplatin group drugs does not cause thyroid dysfunction.Normal tissue complications of cisplatin effect on rapidly proliferating cells(mucosa and bone marrow) leads to mucositis and bone marrow depression. Thyroid is late responding tissue its effect on cisplatin is not known. In our study group population hypothyroidism more in chemo RT group, the cause for this is not known, should be studied in future .

The impact of adjuvant chemotherapy treatment on the risk of development of hypothyroidism in head &neck malignancies is studied by both **Kanti(15) et al** and **Sinrad (16)et al** found that no effect of chemotherapy in thyroid gland dysfunction.

SITE OF PRIMARY TUMOR

SITE OF PRIMARY TUMOR	SUBCINICAL HYPOTHYROID	CLINICAL HYPOTHYROID	NO HYPOTHYROID	TOTAL
SUPRAGLOTIC LAlRYNX	1	0	7	8
NASOPHARYNX	1	1	1	3
ANT2/3TONGUE	3	0	7	10
OROPARYNX	1	1	5	7
HYPOPHARYNX	9	3	10	22
TOTAL	15	5	30	50

Table-5 . Occurrence of hypothyroidism with site of primary.

In our study, 50 patients analyzed and found the hypoparynx malignancy had 12 of 22 patients had hypothyroidism. Followed by Nasopharynx out of 3patients 2 had hypothyroidism, and anterior 2/3 of tongue patients 10 out of 3 had hypothyroidism.

But in our all patients included received whole neck irradiation, so there is primary site is not a risk factor for hypothyroidism. In our study showed 12 patients (24%) developed noted hypothyroidism, The primary site of involvement is varied in literature.

Here in this study primary site of tumor was not a significant factor for developing hypothyroidism, because all the patients made to undergo whole neck irradiation. The exposure of RT to thyroid a was equal in all head& neck cancers , hence we unable to find difference according to the primary site of tumor.

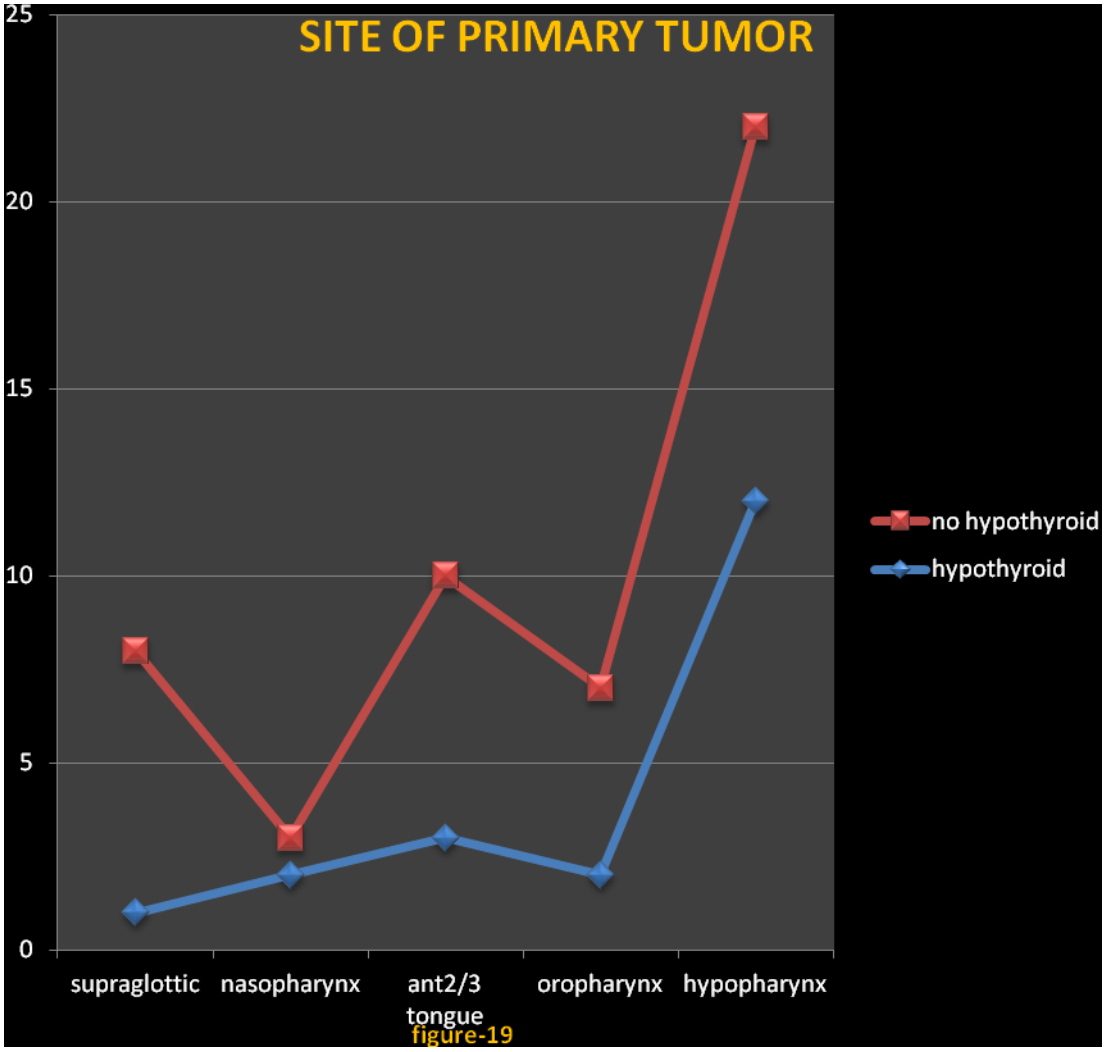


figure-19

In this bar diagram, we can see those lines were parallel.

Hence we come to the conclusion that whenever the frequency was increased the incidence of hypothyroidism was increasing.

RADIATION DOSE:

The thyroid gland tolerance dose **TD5/5 is 20GY** when part or whole thyroid gland irradiated with conventional fractionation.

TD 5/5 : Defined as the radiation dose that could cause not more than 5% severe complication rate within 5yeary is after treatment.

In our study we included 50 patients, all the patients received radical dose to the neck that is 60-66gy. 38(76%) patients received 60gy RT, 12(24%) received 66gy RT, by conformal technique.

The mean dose thyroid gland irradiation is 59GY.Which is more than tolerant dose of thyroid gland leads to its ablation and causing hypothyroidism. The mean dose thyroid gland irradiation is 59GY.Which is more than tolerant dose of thyroid gland leads to its ablation and causing hypothyroidism.

ONSET OF HYPOTHYROIDISM

In our study we conducted for one year duration, we found out 20(40%) patients developed hypothyroidism following RT to neck. Among them 12% had subclinical hypothyroidism at6months ,18%had subclinical hypothyroidism at one year.In clinical hypothyroidism 4(8%) had at one year.1patient (2%) had hypothyroidism at 6months post RT.

	SUBCLINICAL HYPOTHYROID	CLINICAL HYPOTHYROID
6MONTHS	**6**	**1**
1YEAR	**9**	**4**
TOTAL	**15**	**5**

Table-6.Onset of hypothyroidism with occurrence of hypothyroidism.

We also found that the subclinical and earlier presentation occurs in female gender rather than male. By this study we able to prevent the occurrence of clinical hypothyroidism.

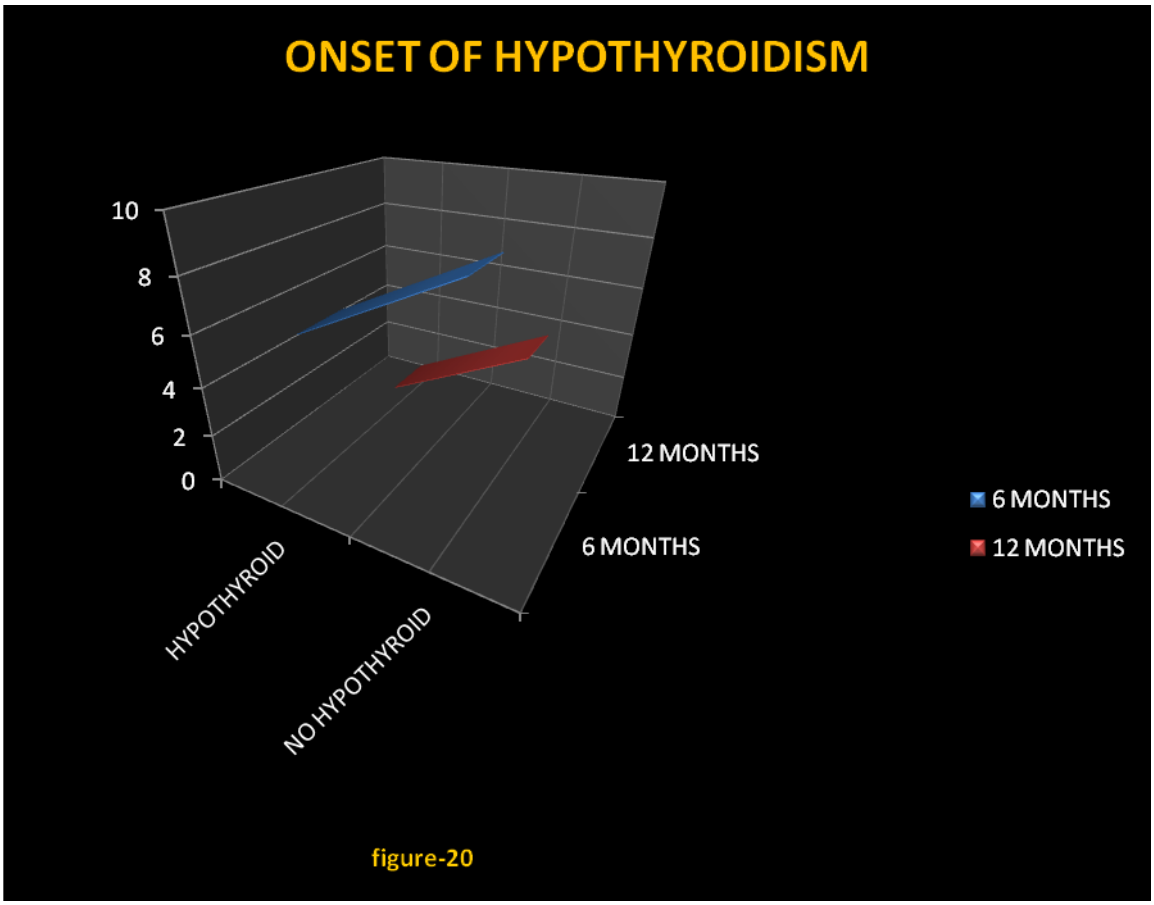


figure-20

In this diagram, subclinical to clinical manifestation developed over a period from 6 months to 1 year.This graph represents the patients affected with subclinical hypothyroidism is more than clinical hypothyroidism in 6months post irradiation, but the clinical hypothyroidism will be more in 1year followup.This shows the progression of subclinical to clinical hypothyroidism is more in one year follow up.

7. DISCUSSION

The effects of ionizing radiation on thyroid gland in therapeutic neck irradiation (40-70GY) leads to hypothyroidism. The impact of post irradiation hypothyroidism first reported in 1929[1].The first reported case of hypothyroidism in patients treated for head &neck malignancy reported in literature on 1961[(16)]

Most of literature review quoted that the incidence of hypothyroidism following RT have ranged from 3 to 47%. Most of the studies states that the incidence is between 20 to 30% .(17).

In our study shows 40% incidnce of hypothyroidism comparable with literature reported above.

In our study we detected the incidence of hypothyroidism in cases 40% and controls 0%,.

Among 40%,the subclinical hypothyroidism is 30% and the clinical hypothyroidism is 10%, but in control arm none of the patient had hypothyroidism,

which clearly states that the radiation to the neck and radiation dose are the risk factor for causing hypothyroidism

The following studies shows the incidence of hypothyroidism.

1. 1.Study done by **Einhorn and Wikhokins** ,for the periods of 10yrs of follow-up in 45pts treated with radiation for carcinoma of larynx and hypo pharynx, they evaluated the incidence of hypothyroidism is 7.3%.This is one of the longest study[18].

2. **Glastin et al** the high incidence of hypothyroidism in patients treated for malignant lymphomas with significant Pvalue (<0.05)[19.]

3. 3.**Alterio et al** stated that among different types of radiation induced thyroid disorders hypothyroidism is the commonest late effect with the incidence of 20 to 30%[20].

In our study we found out 40% incidence of hypothyroidism with one year post radiation followup.

INCIDENCE OF HYPOTHYROIDISM COMPARING WITH STUDIES

	incidence	
Einhorn and Wikhokins	**7.3 %**	
Emami et al	**35%**	
Alterio et al	**20-30%**	
Our study	**40 %**	
Srikantia et al	**42%**	

Table-7 .INCIDENCE OF HYPOTHYROIDISM COMPARING WITH STUDIES

In our study the followup period was on year post radiation, which is lower than other studies.Study conducted by **Srikantia et al** for the period of 9months in 45patient showed 42% had hypothyroidism.

Our study showed comparable results with the above study. In our study 14% developed hypothyroidism at 6months of post RT follow-up and 36% had hypothyroidism at 0ne year follow-up of post RT, Among them the clinical hypothyroidism is 10% that is 2% in 6months follow-up and 8% in 1yr follow-up.

In our study more incidence of subclinical hypothyroidism at one year follow-up. Though it is not statically significant detecting hypothyroidism at early stage and prevent progression to clinical hypothyroidism prevent the complications and further consequences of hypothyroidism. The study by **Wickams et al** showed that patients with subclinical hypothyroidism progress to clinical hypothyroidism 38times more risk.

SEX RATIO AND AGE ANALYSIS.

In our study 10 out of 39 males were found to have hypothyroidism , and in females 10 out of 11 were affected. Though the smaller sample size, the females are affected more than males. But in our control none of the patient had hypothyroidism even though all the patients were females, this is once again proven that the neck irradiation is the risk factor.

The study done **Weichsel begum RR et al** showed the incidence of hypothyroidism more in female like general population[21].In our study the age of patient falling between 25 yrs to >66yrs of age.

The mean age of males is 52yrs and the mean age of females were 59 yrs.6 patients

developed hypothyroidism in patient with <50 yrs of age and 51-65 yrs 14 patients had Hypothyroidism. this denotes patient with the elderly age group affected more compared to younger and older age group, this is identical with the study done by Mercado et al[22].

In our study the age and sex was of statically significant with other studies.The higher incidence among female patients described by Posner et al and Hancock et al with the incidence of hypothyroidism is 20%, the relative risk of 1.6:1 in females[21,23].

The reason for hypothyroidism common in neck irradiated female patients:

1.Autoimmunity:

Radiation induced hypothyroidism is a organ specific autoimmune disorder, causing epithelial damage as well as necrotizing vacuities and thrombosis. Injury to the epithelial tissue leads to release of thyroid cellular components that acts as a triggering antigenic stimulus leads to production of organ specific Auto antibodies and leads to initiation of autoimmune process and thyroid dysfunction. In autoimmune mechanism their must by sustain release of auto antibody following antigenic stimuli a genetic susceptibility must be present.

In **females** it is present in **Ir-1** lies within the majorhistocompatibility complex.

In **males** it is **HLA-8** association has been demonstrated for autoimmune mechanism.**Tamura et al** demonstrated raised antibody titre following irradiation then they subsequently become hypothyroid.

2.Vascular damage

Leads to necrotizing vasculitis and thrombosis.

3.Parenchymal damage

Leads to thyroid dysfunction by epithelial injury and destruction of Parenchyma.

COMPARING PRIMARY SITE OF TUMOR WITH STUDIES:

In our study the highest percentage of hypothyroidism in hypopharyngeal and cancer with the percentage of 24% and another study showed highest percentage in laryngeal cancers.The study done by Aich et al had the above resulst[24]

In our study	24%
Aich et al	17%

Table-8.occurence of hypothyroidism with site of primary

Primary site of tumor was not the tumor not statiscally significant, because all the patient had whole neck irradiation received same dose of radiation to thyroid gland.

CONURRENT CHEMORADIATION VS RADIATION:

Out 50patients studied 35 patients received concurrent chemo radiation and 15 received only radiotherapy. Among 35 in concurrent CT+RT group 18(36%) had hypothyroidism.

Only RT group 2(4%) out of 15 had hypothyroidism

The use of chemotherapy varies in manyinsitutionsforforlocallyadvanced head &neck malignancy , in our institute concurrent chemotherapy used in locally advanced head and neck cancers to improve the local control and improve the overall survival.

In our study 70% of patients receiving concurrent chemo radiotherapy were included and 30% of receiving only radiotherapy included.

Turner et al and Mercado et al showed highest percentage of hypothyroidism in concurrent chemo radiotherapy group, which is same as our study (2,22).

Turner et al showed 77% had hypothyroidism, Mercado et al showed 50% had hypothyroidism

Aich et al had 21% incidence of hypothyroidism with concurrent radiation and RT received patients only 16%had hypothyroidism (23).

Occurrence of hypothyroidism with concurrent chemoRT

Aich et al	21%
In our study	36%
Turnr et al	36%

Table-9 . Occurrence of hypothyroidism with concurrent chemoRT

RADIATION DOSE COMPARING WITH STUDIES:

	RT DOSE GIVEN	MEAN THYROID DOSE
SRIKANTIA et al	**>60GY**	**57GY**
IN OUR STUDY	**60-66GY**	**59GY**

Table 10-Radiation dose comparing with studies.:

Srikantia et al they studied 45 patients receiving radiotherapy to neck 64.4% received >60gy RT to neck and the mean dose was 60gy,in our study among 50 patients 76% received >60gy RT ,the mean dose was 59 Gy which is comparable with above study.

Onset of hypothyroidism

In our study 6patients developed subclinical hypothyroidism at 6months,and 1patient developed clinical hypothyroidism at 6months post RT.

9 patients developed subclinical hypothyroidism at one year and 4patients developed clinical at hypothyroidism at one year. These results are comparable with other studies.

And also in our study most of patients developed subclinical and clinical in one year post RT, compared to 6months following radiation.

Study done by Wichams showed post RT to neck showed patients with subclinical hypothyroidism had 38% risk of progression to clinical hypothyroidism(24).

Aich et al noticed hypothyroidism at 6weeks post RT, With concurrent chemo radiotherapy they had hypothyroidism at 6months post RT. The high incidence of hypothyroidism at 2years 20%.

All of the studies stated that recognizing subclinical hypothyroidism at a early stage and treating the same with thyroxin prevents of clinical hypothyroidism, and also preventing cardiac events by reducing lipid level, as mentioned by **cooper et al(26).**

Tell et al study quoted lifelong Thyroid function testing in long term survivors of head& neck patient necessary, because the incidence of hypothyroidism time and even after long term follow up(27).

8. CONCLUSION

Hypothyroidism (clinical or subclinical) is an under rated, neglected under-recognized morbidity of external beam radiotherapy to neck. In our study included 50 patients with head and neck cancers, 20 out of 50 had abnormal thyroid values, among which 15out of 50 had subclinical hypothyroidism and 5 out of 50 patients had clinical hypothyroidism.

The factors associated with the development of hypothyroidism as following:

1. Radiation neck >40 Gy
2. Female Sex
3. Post RT duration.
4. Concurrent chemo radiation.

The radiation to the neck is the only predictive factor which strongly associated with development of hypothyroidism. It is proven in our study by controls who doesn't received radiation to neck, not developed thyroid dysfunction.

Our analysis also found out, female patients progressed to clinical hypothyroidism fast compared to male sex. It is also proven that female sex hypothyroidism occurs earlier than males.

In concurrent chemo radiotherapy group also had higher percentage of hypothyroidism. The reason why in the concurrent radiotherapy group had hypothyroidism is not known, but may be because cisplatin is a radio sensitizer and it enhances the effect of radiation, but it doesn't cause thyroid dysfunction per se. Even though it is statistically significant, hence because the sample size is small, we need a separate study to ascertain this phenomenon, as the sample in our study is small.

We also detected the incidence of **hypothyroidism increasing with time**, the progression of subclinical hypothyroidism to clinical hypothyroidism occurring with increasing time. So identifying subclinical hypothyroidism at an early stage and treating with appropriate thyroxin supplementation prevent progression to clinical hypothyroidism and its related morbidity.

Hereby we strongly recommend,

1. 1.Thyroid function tests should be made routine during follow ups from as early as 6weeks and carried out lifelong for long term survivors.

2. It is mandatory to keep thyroid function test as a routine for all the patients receiving neck irradiation.

3. All patients reviewed by endocrinologist regularly will improve the patient quality of life.

4. To create awareness in female patients about the possibility of hypothyroidism after radiation

IN FUTURE

1. We recommend this study with large sample size and long term regular follow up in long-term survivors.
2. Use of newer technologies like Intensity-Modulated Radiotherapy and shielding of thyroid gland can limit dose to thyroid gland, which may be tried in future to reduce the occurrence of hypothyroidism.
3. Thyroid gland considered as OAR(organ at risk) and give dose constrains to thyroid gland and at the same time dose to target not to be compromised.

9. Bibliography

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. Cancer statistics 2006. CA Cancer JClin. 2006;56:106–30.
2. Turner SL TiverBoyagesSC.Thyroiddysfuction following radiotherapy for head&neckcancer.Int J Radiatoncol Bio Phys 1995;31:279-8.3.
3. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease,in a community: The Wickham survey.ClinEndocrinol (Oxf) 1977;7:481–93.
4. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011; 61:69.
5. Halperin EC, Perez CA, Brady, LW. Preface to the first edition. In: Halperin EC, Perez CA, Brady LW, eds. Perez and Brady's principles and practice of radiation oncology, 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2008:xxi.
6. Awwad HK (2005) Normal tissue radiosensitivity: prediction on deterministic or stochastic basis? J Egypt NatlCancInst 17(4):221–230 (review)

7. Bergonie J, Tribondeau L (1906) Interprétation de quelquesrésultats de la radiothérapieetessaide fixation d'une technique rationelle. C R AcadSci 43:983–98
8. Rubin P, Cassarett G. A direction for clinical radiation pathology. In: Vaeth JM, et al., eds. Frontiers of radiation therapy and oncology VI. Baltimore, MD: University Park Press, 1972:1–16.
9. Baumann M, Petersen C, Krause M (2005) TCP and NTCP in preclinical and clinical research
10. Larsen .Williams Textbook of Endocrinology.10th ed. W B Saunders, Philadelphia, an imprint of Elseivers2003.
11. Bergonie and FelixH,DupreM,CourtL.Longterm influence of radiotherapy for cancers of larynx on the appearence of myxedema.Lyon Med 1961;1043-50.
12. Nishiyama K, Tanaka E, Tarui Y, Miyauchi K, Okagawa K. A Prospective analysis of subacutethyroiddusfunction after neck irradiation.Int J RadiatOncolBiol Phys. 1996;34:439–44.
13. BonatoC,serverinoRF,ElnecaveRH.Reduced thyroid volume and hypothyroidism in survivors treated with

radiotherapy.JPediatrEndocrinol Metab.2008.,21:943-9.doi: 10.1515/JPEM.2008.21.10.943.

14. Colevas AD, Read R,Thornhill J ,A dakS, Tishler R,Busse P,etal. Hypothyroidism incidence after multimodality treatment stage III and IV Squamous cell carcinoma of head and neck .Int J RadiatOncotBiolPhys 2001:51:599-604.

15. Kanti AA Ranjan DA Santhanu P. et al .Iatrogenic hypothyroidism:A consequences of external beam radiotherapy to head&neckmalignancies.J Cancer Res Ther.200;:1:142-146.doi:10.4103/0973-1428.19593(PUBMED)(Cross Ref)

16. Sinrad RJ,TobinEJ,Mazaferri EL et al.Hypothyroidsm after nonthyroidhead&neck k cancer.ArchOtolarngol Head Neck Surg.2000;126:326-328.

17. Leining A, Ducan NO, Black eslee DB, Smith DB. Hypothyroidism following radiation therapy for head and neck cancer Otolaryngol Head and neck Surg 1990;103;10-3.

18. Biondi B, Fazio S, Palmieri EA, Carella C, Panza N, Cittadini A, et al. Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. J ClinEndocrinolMetab. 1999;84:2064-7

19. Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, et al. Subclinincal hypothyroidism and the risk of heart failure, other cardiovascular events and death. Arch Intern Med. 2005;165:2460–6.

20. Alterio D, Jereczek-Fossa BA, Franchi B, D'Onofrio A, Piazzi V, Rondi E, et al. Thyroid disorders inpatients treated with radiotherapy for head-and-neck cancer: A retrospective analysis of seventy-threepatients.Int J RadiatOncolBiol Phys. 2007;67:144–50.

21. Posner MR,Ervin TJ Miller D,FabinRL,Norris CM JR Weichelbaum RR et al.Incidence of hypothyroidism following multimodality for advanced squamous cell carcinoma of head and neck cancer.Laryngoscope 1984;4:451-54.

22..Mercado G Adalstein DJ, Saxton JP, Secic M,Larto MA, Lavertu P.Hypothyroidism a frequent event after radiotherapy and radiotherapy with chemotherapy for patients with head and neck carcinoma.Cncer 2009;92:2892-7.

23. Hancock SL, McDougall IR, Constine LS. Thyroid abnormalities after therapeutic external radiation.IntJRadiatOncolBiol Phys. 1995;31:1165–70.

24. Aich RK, Deb AR, Pal S, Naha BL, Ray A. Latrogenic hypothyroidism: A consequence of external beam 8/16/2014 How common is hypothyroidism after external radiotherapy to neck in head and neck cancer patients?http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3342720/ 14/14 radiotherapy to the head neck malignancies. J Cancer Res Ther. 2005;1:142–6.
25. Sinard RJ, Tobin EJ, Mazzaferri EL, Hodgson SE, Young DC, Kunz AL, et al. Hypothyroidism aftertreatment for nonthyroid head and neck cancer.ArchOtolaryngol Head Neck Surg. 2000;126:652–7.
26. Cooper DS. Subclinical Hypothyroidism. N Engl J Med.2001;345:260–5.
27. Tell R, Lundell G, Nilsson B, Sjödin H, Lewin F, Lewensohn R. Long term incidence of hypothyroidismafter radiotherapy in patients with head and neck cancer. Int J RadiatOncolBiol Phys. 2004;60:395–400.
28. Liening DA, Duncan NO, Blakeslee DB, Smith DB. Hypothyroidism following radiotherapy for head andneck cancer. Otolaryngol Head Neck Surg. 1990;103:10–3.

KEY WORDS:

- Head& neck cancer, concurrent chemo radiotherapy, hypothyroidism, Radiotherapy.